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Intermittent peritoneal dialysis in the treatment of experimental salicylate intoxication

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SALICYLATE intoxication and the resulting alterations in body chemistry represent a complex and serious metabolic disturbance. An excellent review and critical analysis of the nature of the electrolyte disturbances which result from salicylate intoxication has been published recently by Winters.[1]

Correction of the electrolyte imbalances with *judicious* use of parenteral fluids is important in the management of severe intoxication.[2] However, when life-threatening manifestations are encountered, treatment should also be directed toward removing salicylate from the body as promptly and safely as possible. Exchange transfusions[3, 4, 5] and extracorporeal hemodialysis[6, 7] (artificial kidney) are two effective methods, but both have certain limitations. While the "artificial kidney" is an efficient device for ridding the body of salicylate, its safe operation requires an active, readily available team of highly trained personnel and its use therefore is limited primarily to medical centers. Further-

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more, use of this procedure may be technically impossible in infants under 24 months of age, the age group in which the majority of deaths from salicylate intoxication occur.

Exchange transfusion is a relatively simple procedure, but removal of sufficient amounts of salicylate from the body requires exchange with a quantity of blood equal to at least twice the patients' blood volume.[5] Thus, the procedure itself may become a formidable and dangerous one in larger infants and older children. In addition, secondary complications such as tetany and transfusion reactions may occur.

While much of the interest concerning alkali administration for the treatment of salicylate intoxication has been directed toward combating the accompanying metabolic acidosis,[8, 9] alkalinization of the urine has been known for a number of years to increase the renal excretion of salicylate.[10, 11, 12] Recently, carbonic anhydrase inhibitor, through its ability to alkalinize the urine by blocking tubular ion exchange and reabsorption, has been demonstrated to increase the urinary excretion of salicylate in normal humans and experimental animals.[12, 13] Kaplan and del Carmen,[13] as a result of animal studies, emphasized the danger associated with the use of carbonic anhydrase inhibitor and suggested its possible use in early salicylate intoxication with careful concomitant administration of sodium bicarbonate. Its use in the treatment of human salicylate intoxication, however, is reported[14] to be associated with an increased incidence of neurological complications despite careful control of acid-base balance.

Intermittent peritoneal dialysis is a safe and simple procedure which does not require elaborate equipment and, if necessary, can be continued for days.[15, 16] To our knowledge, there is no record in the literature concerning the use of this procedure in the treatment of salicylate intoxication in either humans or experimental animals.

We wish to report the results of a study in which intermittent peritoneal dialysis was used in the treatment of experimental salicylate intoxication in dogs. Several types of dialyzing fluid were evaluated including (1) modified Grollman's solution with 1.5 and 3 per cent glucose (used with and without concomitant administration of parenteral fluids); (2) heparinized pooled dog plasma; and (3) 5 per cent human albumin in a buffered diluent rendered iso-osmotic with plasma (Albumisol*). This solution is stabilized with 0.004 M sodium caprylate and 0.004 M sodium acetyltryptophanate containing no preservative.

GENERAL EXPERIMENTAL PLAN AND PROCEDURES

Mongrel dogs in a good state of nutrition were used; the last feeding was not more than 6 hours prior to the experiment. In preliminary experiments, a single intravenous injection of 250 mg. per kilogram of sodium salicylate as a 2.5 per cent solution was found to be the optimal dose for the purpose of these experiments. Following administration of the sodium salicylate, a 1 hour equilibration period was employed before dialysis procedures were instituted. Blood salicylate levels prior to peritoneal dialysis ranged from 42 to 83 mg. per cent and signs of severe salicylate intoxication such as hyperpnea, nausea, vomiting, defecation, ataxia, irritability, and depression were present in all animals.

The following experimental groups were studied: Group I, 3 dogs dialyzed with a modified Grollman's solution; Group II, 2 dogs dialyzed with a modified Grollman's solution and concomitant administration of intravenous fluids; Group III, 4 dogs dialyzed with pooled dog plasma; Group IV, 3 animals dialyzed with 5 per cent human albumin in a buffered diluent (Albumisol).

Dialysis Procedure. Following is a general description of the dialyzing technique employed in these experiments: A No. 16F Ochsner's trocar was inserted through a small midline skin incision at a point two-thirds the distance from the xiphoid process to the symphysis pubis; with the stylet in place, the trocar was forced through the ab-

*Albumisol used in these studies was supplied by Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa., through the courtesy of Dr. Richard T. Smith.

dominal wall into the peritoneal cavity; the stylet was then removed and a No. 14F. multiperforated plastic catheter was threaded through the trocar and directed into the pelvic gutter for a distance of approximately 12 inches; the trocar was removed and the catheter was fixed in place with mattress sutures, a procedure which helped to prevent leakage; dialyzing fluid was instilled and removed by gravity.

Blood samples and samples of the dialyzing fluid in the peritoneal cavity were obtained for chemical analyses at 60 minute intervals.

Chemical Analyses. Plasma and dialyzing fluid concentration of salicylic acid were determined by a micromodification of the technique described by Brodie.[17]

Sodium and potassium determinations were carried out by flame photometry with the use of an internal standard. The calcium was determined by titration with EDTA.[18]

Total proteins and albumin were determined by the biuret method.[19]

SPECIFIC PROCEDURES AND RESULTS

Experimental Group I. Three dogs were dialyzed with Grollman's solution having a glucose concentration of 15 Gm. per liter, to which 4 mEq. per liter of potassium as potassium chloride was added. Dogs E and F (Table I) were dialyzed 3 times with an equilibration period of 60 minutes per lavage. The volume of fluid employed for each lavage was 1,000 and 1,200 c.c., respectively. Dog G was dialyzed 4 times using 1,500 c.c. of fluid for each lavage. Plasma salicylate levels 1 hour after administration of salicylate and prior to instillation of the lavage fluid were 58, 48, and 60 mg. per cent, respectively. The plasma samples obtained at hourly intervals showed a gradual decrease in the salicylate concentration. A decrease of 23 mg. per cent occurred at the end of 3 hours (3 lavages) in dogs E and F, and 30 mg. per cent in dog G after 4 hours (4 lavages).

In each of the dogs, the concentration of salicylate in the dialyzing fluid was essentially the same at the end of the first and second lavages. After the first 2 lavages, the efficiency of the dialyzing procedure in the removal of salicylate decreased remarkably as indicated by the disproportionate decrease in concentration of salicylate in the dialyzing fluid in comparison to that of the plasma. The total salicylate removed in the 3 dogs was 250, 200, and 290 mg., respectively, which represented 6.9, 6.2, and 7.1 per cent of the dose of salicylate administered. Urine and fecal salicylate excretions were not followed in any of the groups in these acute experiments.

Hematocrits were measured at the beginning and end of the experiment in dogs F and G, and had increased 9 and 15 per cent, respectively.

Experimental Group II. This group consisted of 2 dogs. The dialyzing fluid differed from that used in Group I in that the final glucose concentration was increased to 30 Gm. per liter. The same dialyzing technique was employed. In addition, these animals re-

Table I. Effect of intermittent peritoneal dialysis with modified Grollman's solution on salicylate removal

			Peritoneal dialyses			*Concentration salicylate lavage fluid (mg. %)*				*Salicylate removed*	
Animal	*Weight (Kg.)*	*Hourly plasma salicylate concentration (mg. %)*	*Volume c.c./ lavage*	*Number lavages*	*Duration each lavage (hr.)*	*Lavage 1*	*Lavage 2*	*Lavage 3*	*Lavage 4*	*Total (mg.)*	*Per cent administered dose*
E	14.4	58, 49, 45, 35	1,000	3	1	11.1	11.1	3.9		250	6.9
F	13.0	48, 35, 28, 25	1,200	3	1	6.3	5.0	3.7		200	6.2
G	16.4	60, 40, 38, 34, 30	1,500	4	1	8.0	10.6	1.5	0.7	290	7.1

Table II. Effect of intermittent peritoneal dialysis with modified Grollman's solution and concomitant parenteral fluid administration on salicylate removal

			Peritoneal dialyses			Concentration salicylate lavage fluid (mg. %)				Salicylate removed	
Animal	Weight (Kg.)	Hourly plasma salicylate concentration (mg. %)	Volume c.c./ lavage	Number lavages	Duration each lavage (hr.)	Lavage 1	Lavage 2	Lavage 3	Lavage 4	Total (mg.)	Per cent administered dose
10	9	45, 32, 27, 25, 24	1,270	4	1	11.6	9.2	4.5	1.3	344	15.3
11	6	42, 28, 26, 20	600	3	1	5.9	5.2	3.5		108	7.2

Table III. Effect of intermittent peritoneal dialysis with heparinized pooled dog plasma on salicylate removal

			Peritoneal dialyses			Hourly concentration salicylate lavage fluid (mg. %)		Salicylate removed	
Animal	Weight (Kg.)	Hourly plasma salicylate concentration (mg. %)	Volume c.c./ lavage	Number lavages	Duration each lavage (hr.)	Lavage 1	Lavage 2	Total (mg.)	Per cent administered dose
12	16.3	57, 61, 52, 48, 45	1,000	1	4	21, 41, 30, 38		350	8.6
18	7.7	83, 78, 65, 58, 55	385	1	4	39, 56, 63, 54		200	10.4
14	11.2	63, 55, 46, 37, 33	1,750	1	4	14, 15, 22, 22		380	13.6
13	14.8	83, 68, 48, 47, 49	850	2	2	29, 47	29, 44	760	20.5

ceived an intravenous infusion of a 5 per cent glucose solution containing hypotonic amounts of electrolytes, i.e., 40 mEq. of sodium, 35 mEq. of potassium, 50 mEq. of chloride, and 25 mEq. of lactate per liter. Theoretically, increasing the osmolarity of the dialyzing fluids combined with the intravenous administration of a solution containing hypotonic amounts of electrolytes should promote diffusion of plasma water and the diffusable salicylate contained therein into the dialyzing fluid present in the peritoneal cavity.

The data obtained in these animals (Table II) concerning plasma and lavage fluid salicylate concentrations were quite similar to those obtained in the Group I animals. Plasma salicylate levels were 45 and 42 mg. per cent, respectively, prior to dialysis, and at the end of final dialysis period were 24 mg. and 20 mg. per cent, respectively. The concentration of salicylate in the lavage fluid at the end of the first 2 dialyses remained approximately the same in each dog, as was the case in the animals of Group I. The salicylate concentration in the lavage fluid in dog 10 decreased appreciably at the end of the third and fourth lavages, again indicating a decrease in the efficiency of the dialyzing procedure, such as was noted in Group I. The total salicylate removed in dog 10, which received 4 lavages of large volume, was 344 mg. or 15.3 per cent of that administered, and in dog 11, which received 3 lavages with volumes of solution comparable to that used in Group I, was 108 mg. or 7.2 per cent of that administered.

Hematocrits in these animals each increased about 9 vol. per cent, and indicated moderate hemoconcentration.

Experimental Group III. The dialyzing medium employed in this group of 4 animals consisted of heparinized pooled dog's plasma. The volume instilled in each lavage, with the exception of dog 14, was approximately equal to that of the calculated plasma vol-

ume of the animal (5 per cent body weight). The heparinized plasma was allowed to equilibrate for a period of 4 hours before removal in dogs 12, 14, and 18. Dog 13 was dialyzed twice with equilibration periods of 2 hours each. The equilibration times were increased beyond an hour in this group in anticipation that protein binding would result in a progressive increase of salicylate concentration in the lavage fluid. The plasma salicylate concentrations prior to, and at the end of, the dialyses (Table III) were somewhat higher than in Groups I and II (Tables I and II). The greater salicylate concentrations present in the dialyzing fluid used in the animals of Group III suggests, however, that the plasma-lavage fluid was more efficient in removing salicylate than the dialyzing fluids employed in Groups I and II; furthermore, in contrast to Groups I and II, the salicylate concentrations in the plasma-lavage fluid approximated those found in the circulating plasma at the end of the dialysis period.

Although peak salicylate concentrations in the plasma-lavage fluid occurred at the end of 3 hours, Fig. 1 indicates that the greatest increments in salicylate concentration occurred during the first 2 hours. In dog 13, a second lavage also of 2 hours' duration was as effective as the first (Table II and Fig. 1). Interestingly enough, at the end of the second lavage period, the circulating plasma salicylate concentration in this dog was comparable to that of dogs 12 and 18 in which only one-third to one-half as much salicylate had been removed. The total salicylate removed in dogs 12, 18, and 14 was

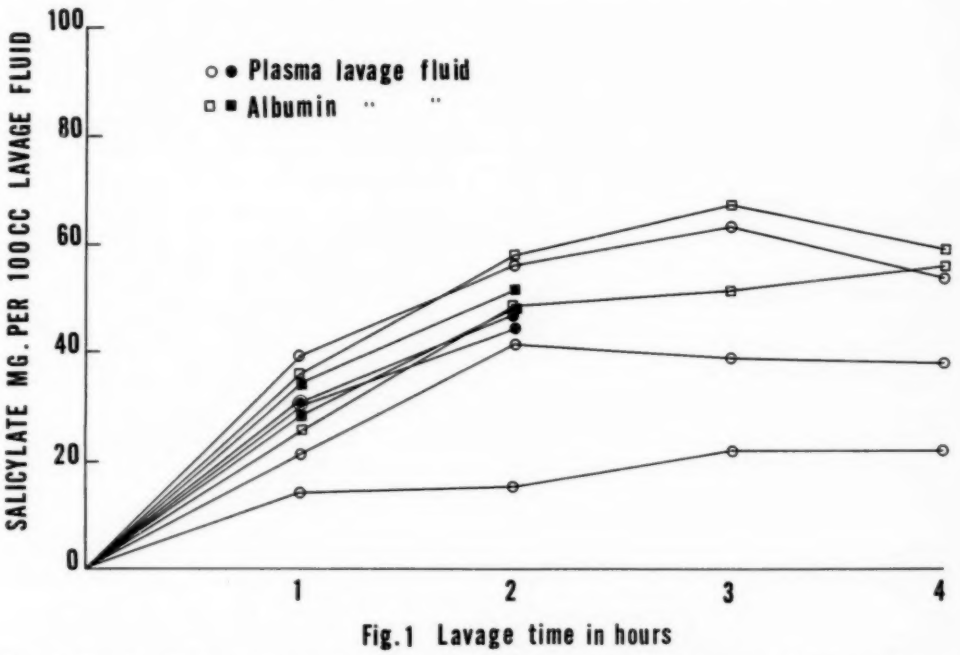

Fig. 1. Hourly salicylate concentrations in the heparinized pooled dog plasma and 5 per cent human albumin in iso-osmotic buffered diluent, which were used as dialyzing media in animals of Group III and Group IV.

■● represent concentrations in lavage fluid in dog 13 and dog 16, which received two lavages of 2 hours' duration; □ ○ represent concentrations in lavage fluid after single 4 hour lavage periods in dogs 12, 14, 15, 17, and 18. The lowest concentrations were found in dog 14, which was dialyzed with the pooled dog plasma that had the lowest albumin concentration. Note that the greatest increment in salicylate concentration occurred during the first 2 hours of dialysis and that two lavages of 2 hours' duration resulted in similar concentrations of salicylate in the lavage fluid.

8.6, 10.4, and 13.6 per cent of that administered. In dog 13, which received 2 lavages, 20.5 per cent of the administered salicylate was removed and represented an appreciably greater removal of salicylate in comparison with that removed from the animals which received multiple 1 hour lavages using Grollman's solution, or a single 4 hour lavage using plasma as the dialyzing fluid.

Of further interest is animal 14, in which the salicylate concentration in the plasma-lavage fluid after 4 hours of equilibration was 22 mg. per cent, the lowest in this group of animals. Table V shows that the albumin concentration of the plasma-lavage fluid used for dialysis in this dog was only 2.8 Gm. per cent. On the other hand, the plasma-lavage fluid used in dog 18 contained the highest concentration of salicylate, 54 mg. per cent. Reference to Table V also reveals that the albumin concentration of the plasma-lavage fluid employed in this animal was greater (5.0 Gm. per cent) than that in plasma-lavage fluids employed in the other animals of this group.

Experimental Group IV. This group consisted of 3 animals, numbers 15, 16, and 17. The lavage fluid used in this group was 5 per cent human albumin in iso-osmotic buffered diluent (Albumisol). Similar to 3 of the 4 animals dialyzed with pooled plasma, the quantity of dialyzing fluid employed was equal to the calculated plasma volume. Dogs 15 and 17 were lavaged one time and the fluid was permitted to equilibrate in the peritoneal cavity for 4 hours. In dog 16, 2 successive 2 hour lavage periods were employed (Table IV).

Plasma salicylate levels were reduced from 64, 61, and 53 mg. per cent to 38, 43, and 36 mg. per cent, respectively. The salicylate concentrations in the lavage fluids of these animals were strikingly higher than those found in the groups treated with Grollman's solution and similar to the highest value obtained in animal 18 of Group III, which was dialyzed with the pooled plasma containing 5 Gm. per cent of albumin. The final salicylate concentration in the lavage fluid was 59 and 56 mg. per cent in dogs 15 and 17 after a single 4 hour dialysis period, and 48 mg. per cent and 51 mg. per cent in dog 16 after 2 dialysis periods of 2 hours each (Table IV). These concentrations were higher than those present in the circulating plasma at the end of the lavage periods. As was the case in animal 13 of Group III (Table III and Fig. 1), a 2 hour period of lavage in dog 16 was virtually as effective as the 4 hour period of lavage in the other 2 animals in Group IV. Furthermore, a repeat lavage of 2 hours' duration removed approximately the same amount of salicylate as the first lavage of similar duration. The total salicylate removed in the animals dialyzed 1 time for a 4 hour period was 11.5 per cent and 10.8 per cent of total dose administered, while that removed in the animal lavaged 2 times for periods of 2 hours each was 19.3 per cent of the administered dose.

DISCUSSION

Schreiner and associates[7] in in vitro experiments employing *continuous dialysis* with a modified Kolff apparatus demonstrated that

Table IV. Effect of intermittent peritoneal dialysis with 5% human albumin in iso-osmotic buffered diluent on salicylate removal

Animal	*Weight (Kg.)*	*Hourly plasma salicylate concentration (mg. %)*	*Peritoneal dialyses*			*Hourly concentration salicylate lavage fluid (mg. %)*		*Salicylate removed*	
			Volume c.c./ lavage	*Number lavages*	*Duration each lavage (hr.)*	*Lavage 1*	*Lavage 2*	*Total (mg.)*	*Per cent administered dose*
15	11.8	64, 53, 46, 40, 38	590	1	4	36, 58, 67, 59		340	11.5
17	12.0	61, 53, 45, 43, 43	600	1	4	25, 48, 51, 56		325	10.8
16	10.5	53, 47, 48, 37, 36	525	2	2	35, 51	28, 48	507	19.3

Table V. Protein concentrations in circulating plasma and lavage fluids

Animal	Plasma proteins (Gm. %)		Albumin concentration Gm./100 c.c. lavage fluid	
	Total	Albumin	Before dialysis	After dialysis
12	6.9	5.0	3.3	3.1
13	6.2	4.2	3.3	3.2
14	6.6	4.0	2.8	2.7
18	5.8	3.3	5.0	5.1
15	4.9	3.3	5.0	5.1
16	5.3	3.5	5.1	5.3
17	5.8	4.2	5.1	5.2

salicylic acid added to plasma and presumably protein bound in part, or salicylic acid added to saline was removed with equal efficiency. We anticipated, on the basis of theoretical considerations regarding the diffusible and nondiffusible protein-bound salicylate fractions known to be present in the circulating plasma, however, that Grollman's solution would be less efficient in removing salicylate by means of *intermittent peritoneal dialysis* than albumin-containing solutions. This proved to be the case.

The difference in the salicylate values between the circulating plasma and the lavage fluids in animals of Groups I and II (Table I and II) suggests that a major portion of the salicylate present in the circulating plasma was nondiffusible. This suggestion is corroborated by the observations of other investigators[11, 12, 20, 21, and 22] who demonstrated that 50 to 80 per cent of the plasma salicylate is nondiffusible when blood levels are comparable to those which prevailed in these experiments. The salicylate concentrations found in the dialyzing fluid at the end of the first two lavage periods in the animals in Groups I and II do suggest, however, that the diffusible fraction present in the circulating plasma and the Grollman's solution in the peritoneal cavity reached an equilibrium within 2 hours. We have no explanation from our data for the low levels of salicylate found in the dialyzing fluid of these animals after the third and fourth lavage periods at a time when relatively high plasma total salicylate levels were present.

The experiments involving the use of lavage media containing albumin (dog plasma and Albumisol) constituted the most interesting ones and may influence treatment of salicylate intoxication in humans. A review of the results presented in Tables III and IV and Fig. 1 clearly demonstrates the removal of large quantities of salicylate by relatively small volumes of fluids containing albumin. The more efficient removal of salicylate by these fluids can be explained by the ability of albumin to bind salicylate, as indirectly suggested in the abstract by Odell.[23]

These data (Fig. 1) further demonstrate a linear increase in the concentration of salicylate in the dialyzing fluid during a 2 hour equilibration period with the result that repetition of the procedure therefore doubled the quantity of salicylate removed (Tables III and IV). Tables III, IV, and V also indicate that the quantity of salicylate present in the dialyzing fluids containing albumin (plasma and Albumisol) is related to their albumin concentration. Thus, the salicylate concentrations were correspondingly high and low in the lavage fluid of the dogs which were dialyzed with the pooled plasma having the highest and lowest albumin content.

Analyses of the 5 per cent albumin solution before and after dialysis revealed that the sodium content remained iso-osmolar and that potassium ion which was absent prior to

Table VI. Electrolyte level in 5 per cent albumin lavage fluid before lavage and end of lavage and in circulating plasma at end of lavage period

	Lavage fluid (mEq./L.)			Plasma (mEq./L.)		
	Na^+	K^+	Ca^{++}	Na^+	K^+	Ca^{++}
5% albumin solution* (Albumisol)	145	0	.6			
Dog 15	147	3.6	3.6	148	3.6	4.1
Dog 16	150	3.7	3.8	140	3.3	4.4
Dog 17	146	3.1	4.3	150	3.1	5.7

*Cl–	130 mEq. per liter.
Acetyltryptophanate	4 mM. per liter.
Caprylate	4 mM. per liter.

lavage had equilibrated with the plasma potassium (Table VI). This suggests that potassium should be added to the Albumisol, especially if repeated lavages with large volumes of Albumisol are used. In salicylate intoxication, the frequent presence of a preexisting hypokalemia[2, 24] makes this practice mandatory. Also, the calcium is low in the albumin solution and approached equilibration with the plasma calcium at the end of the lavage period. Although calcium was not administered to these animals, one must consider a possible need for this ion. Analysis of the lavage fluid in the animals of Groups III and IV for albumin concentration (Table V) showed no alteration as a result of lavage. This indicates that water was not removed from the animals and that dehydration did not occur. That this was true was corroborated by the measurements of blood hematocrits and urinary output as measured by catheterization, neither of which showed any change.

The clinical course of the animals lavaged with plasma and Albumisol was different from that of the 2 groups treated with Grollman's solution. This was most striking in those animals lavaged twice with one of these albumin-containing fluids. The hyperpnea, lethargy, and ataxia improved and, at the end of 4 hours, the animals had completely recovered with the exception of occasional vomiting; in contrast, most of the animals treated with Grollman's solution still showed a majority of the symptoms of intoxication at the end of 5 hours when they were sacrificed.

The present data do not permit accurate estimation of the quantity of salicylate removed by peritoneal dialysis from the vascular and various extravascular fluid spaces.

No effort was made to influence urinary excretion of salicylate in these experiments, our major concern being the determination of the efficiency of intermittent peritoneal dialysis with various types of fluids as a means of removing salicylate from the body. We recognize, of course, that adequate fluid therapy will favor urinary excretion of salicylate as well as correct fluid volume, concentration, and composition abnormalities.

While we have no experience in the treatment of humans with this method, in our opinion, the data obtained from these experiments strongly support intermittent peritoneal dialysis with an albumin-containing solution in the treatment of human salicylate intoxication when more than general supportive therapy is needed and when extracorporeal hemodialysis or exchange transfusion is not feasible. While the efficiencies of the Albumisol and the heparinized plasma in the removal of salicylate from the body were approximately equivalent, differences between purified human albumin suspensions and human plasma do exist. These differences are important as relating to selection of one of them for treatment of human salicylate intoxication, and, in our opinion, favor the selection of purified human albumin. Thus, pooled human plasma represents a potential reservoir for the hepatitis virus. Furthermore, it has a relatively low albumin concentration because the original blood from which it was obtained was diluted with an anticoagulant solution. In addition, heparinized or citrated plasma contains fibrinogen, which theoretically, at least, might be converted to fibrin within the peritoneal cavity with consequent production of fibrous adhesions. Preparations of the purified human albumin fraction are not only free of fibrinogen, but may be pasteurized so as to inactivate any hepatitis virus that might be present. A further advantage is that the concentration of the albumin is constant and known.

Although the present study was motivated by therapeutic considerations, the results obtained suggested a number of additional studies. These concern the relationship between the salicylate and albumin molecules, e.g., the chemical nature of the bond between the two, the strength of the bond, the factors promoting the binding and release of salicylates by the albumin molecule, and the optimal concentration of albumin in the dialyzing fluid. Such studies are currently under way in our laboratory by one of us (M. J. M.) and Robert Fischer.

SUMMARY AND CONCLUSIONS

Intermittent peritoneal dialysis, according to the technique of Grollman, has been studied as a means of treating salicylate intoxication in dogs.

Several dialyzing media were used as follows: (1) Grollman's solution containing 1.5 or 3 per cent glucose and 4 mEq. per liter of potassium was used in 7 dogs, 3 of which concomitantly received hypotonic electrolyte solution intravenously; the dialyzing periods were 1 hour repeated 3 or 4 times for a total dialyzing period of three to four hours; (2) heparinized pooled dog plasma was used in 3 dogs; the dialyzing periods were of 2 and 4 hours' duration; (3) 5 per cent human albumin in a buffered diluent iso-osmotic with plasma was used in 3 dogs; the dialyzing periods were also of 2 and 4 hours' duration.

Grollman's solution was relatively inefficient in removing salicylate from the body. The concentration of salicylate in this lavage fluid after 1 hour was approximately 20 per cent of the total salicylate concentration of the plasma. After 3 or 4 repeated lavages, only 7 to 15 per cent of the total administered dose of salicylate was removed despite concomitant fluid therapy.

As anticipated, the presence of albumin in the dialyzing fluid (plasma or 5 per cent human albumin) resulted in the removal of relatively large quantities of salicylate despite the use of small volumes. The efficiency of the plasma dialyzing fluid was proportional to its albumin content and comparable to the human albumin when similar concentrations of albumin were present. The concentrations of salicylate in the dialyzing fluid equaled or exceeded the total salicylate concentration of the plasma. Repeat dialyses of 2 hours each proved to be equally effective and resulted in removing 20 per cent of the administered dose of salicylate, approximately twice as much as was removed by a single 2 or 4 hour period of lavage. No evidence of dehydration was noted as measured by hematocrit, protein concentration of the lavage fluid, or urinary output.

Clinical improvement correlated well with the efficiency of the procedure in removing salicylate.

Five per cent human albumin in buffered diluent to which potassium is added to achieve a concentration of 4 mEq. per liter is preferable to pooled plasma. Our results indicate that intermittent peritoneal dialysis with such a modified human albumin solution as the dialyzing medium along with adequate intravenous fluid therapy is worthy of trial in the treatment of severe human salicylate intoxication. This is especially true when extracorporeal hemodialysis or exchange transfusion is not feasible, is contraindicated, or is unavailable.

The animal experimentation was conducted in the Department of Clinical Physiology, Institute of Clinical Investigation, Dr. R. R. Overman, Director. For this privilege we are grateful.

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REFERENCES

1. Winters, R. W., White, J. S., Hughes, M. C., and Ordway, H. K.: Disturbances of Acid-Base Equilibrium in Salicylate Intoxication, Pediatrics **23:** 260, 1959.
2. Winters, R. W.: Salicylate Intoxication in Infants and Children, Pediat. Clin. North America **6:** 281, 1959.
3. Done, A. K., and Otterness, L. J.: Exchange Transfusion in the Treatment of Oil of Wintergreen (Methyl Salicylate) Poisoning, Pediatrics **18:** 80, 1956.
4. Adams, J. T., Bigler, J. A., and Green, O. C.: A Case of Methyl Salicylate Intoxication Treated by Exchange Transfusion, J. A. M. A. **165:** 1563, 1957.
5. Leikin, S. L., LoPresti, J. M., and Pohl, D. R.: Severe Salicylate Intoxication Treated by Exchange Transfusion (Preliminary Report), Clin. Proc. Children's Hosp., Washington, D. C., **15:** 43, 1959.
6. Doolan, P. D., Walsh, W. P., Kyle, L. H., and Wishinsky, H.: Acetylsalicylic Acid Intoxication: Proposed Method of Treatment, J. A. M. A. **146:** 105, 1951.
7. Schreiner, G. E., Berman, L. B., Griffin, J., and Feys, J.: Specific Therapy for Salicylism, New England J. Med. **253:** 213, 1955.

8. Barnett, H. L., Powers, J. R., Benward, J. H., and Hartmann, A. F.: Salicylate Intoxication in Infants and Children, J. PEDIAT. **21:** 214, 1942.
9. Erganian, J. A., Forbes, G. B., and Case, D. M.: Salicylate Intoxication in the Infant and Young Child (Report of 13 Cases), J. PEDIAT. **30:** 129, 1947.
10. Williams, F., and Leonards, J. R.: The Effect of Sodium Bicarbonate on the Renal Excretion of Salicylate, J. Pharmacol. & Exper. Therap. **93:** 401, 1948.
11. Gutman, A. B., Yu, T. F., and Sirota, J. H.: A Study, by Simultaneous Clearance Techniques, of Salicylate Excretion in Man. Effect of Alkalinization of the Urine by Bicarbonate Administration; Effect of Probenecid, J. Clin. Invest. **34:** 711, 1955.
12. Macpherson, C. R., Milne, M. D., and Evans, B. M.: The Excretion of Salicylate, Brit. J. Pharmacol. **10:** 484, 1955.
13. Kaplan, S. A., and del Carmen, F. T.: Experimental Salicylate Poisoning: Observations on the Effects of Carbonic Anhydrase Inhibitor and Bicarbonate, Pediatrics **21:** 763, 1958.
14. Schwartz, R., Fellers, F. X., Knapp, J., and Yoffe, S.: The Renal Response to Administration of Acetazolamide (Diamox) During Salicylate Intoxication, Pediatrics **23:** 1103, 1959.
15. Grollman, A.: Acute Renal Failure, Springfield, 1954, Charles C Thomas, Publisher.
16. Maxwell, M. H., Rockney, R. E., Kleeman, C. R., and Twiss, M. R.: Peritoneal Dialysis, J. A. M. A. **170:** 917, 1959.
17. Brodie, B. B., Udenfriend, S., and Coburn, A. F.: The Determination of Salicylic Acid in Plasma, J. Pharmacol. & Exper. Therap. **80:** 114, 1944.
18. Friedman, Howard S., and Rubin, Martin, A.: Clinical Significance of Magnesium: Calcium Ratio; Technic for Determination of Magnesium and Calcium in Biologic Fluids, Clin. Chem. **1:** 125, 1955.
19. Gornall, A. G., Bardawill, C. J., and David, M. M.: Determination of Serum Proteins by Means of Biuret Reaction, J. Biol. Chem. **177:** 751, 1949.
20. Smith, P. K., Gleason, H. L., and Ogorzalek, S.: Studies on the Pharmacology of Salicylates, J. Pharmacol. & Exper. Therap. **87:** 237, 1946.
21. Chabanier, H., Lebert, M., and Lobo-Onell, C.: De l'Absorption du salicylate de soude par le serum sanguin, Compt. rend. Soc. de biol. **88:** 178, 1923.
22. Bjorneboe, M., Dalgaard-Mikkelsen, S., and Raaschou, F.: On the Excretion of Salicylic Acid in Man (Preliminary Report), Scandinav. J. Clin. & Lab. Invest. **1:** 287, 1949.
23. Odell, G. B.: Protein Binding of Bilirubin and Its Possible Relationship to Kernicterus, Program and Abstracts, Soc. Ped. Research, 29th Annual Meeting, 1959, p. 57.
24. Robin, E. D., Davis, R. P., and Rees, S. B.: Salicylate Intoxication With Special Reference to Development of Hypokalemia, Am. J. Med. **26:** 869, 1959.

Coarctation of the aorta and associated patent ductus arteriosus

I. Experimental studies in dogs

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ST. LOUIS, MO.

WITH THE TECHNICAL ASSISTANCE OF

Charles Crawford, B.S.

DURING the past eight years we have been impressed by the grave prognosis of infants born with the combination of coarctation of the aorta and an intra- or extracardiac shunt. In this same period we have seen approximately 60 infants with these combined malformations who died in spite of intensive efforts to combat the intractable congestive cardiac failure which they developed in the first one or two months of life.[1, 2] Keith[3] has more recently stressed the high incidence of additional cardiac defects, especially patent ductus arteriosus in infants born with coarctation of the aorta, and the frequency with which they develop congestive failure early in the neonatal period. Cooley[4] reported upon the high frequency of pulmonary hypertension in infants and children with this combination of defects and pointed out that the surgical risk is high in this group. We too, as others,[3, 5, 6] feel that surgical treatment is risky but is less so than medical management. In the past 10 years we have salvaged 9 of 17 infants by successful surgical correction of the coarctation of the aorta and patent ductus arteriosus.[7]

There remain certain anatomic and physiologic aspects of this interesting group of patients which still are puzzling:

1. Is it the presence of the intra- or extracardiac shunt with the coarctation of the aorta which predisposes to the congestive failure and death in the neonatal period?

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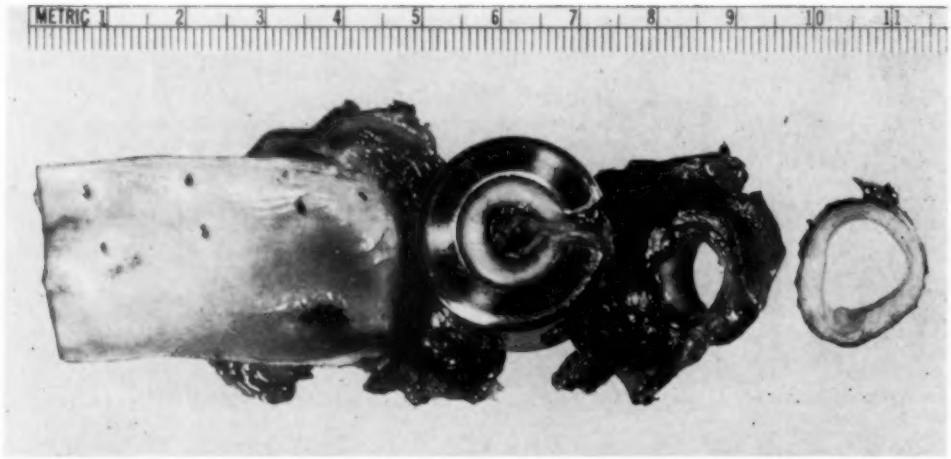

Fig. 1. A postmortem specimen of the aorta with the Ameroid ring in place showing the marked constriction which was achieved.

2. What are the frequency and etiology of the pulmonary hypertension observed in these patients?

3. Patency of the ductus arteriosus is the most frequently associated malformation observed in these patients.[1-5, 8] Does the site of the coarctation, i.e., preductal or postductal, influence the prognosis, or predispose to the development of pulmonary hypertension?

4. What is the pathogenesis of the fibrous intimal thickening of the small pulmonary arteries which has been observed[2, 9] in these infants?

These questions, especially 2 and 4, do not apply solely to this group of patients, and are pertinent and unanswered in cases of other congenital cardiac malformations.

The hemodynamics of coarctation of the aorta with an extracardiac shunt were studied in acute experiments on dogs by Gupta and Wiggers.[10, 11] In an effort to simulate the clinical picture presented by this group of patients and to try to answer the questions raised, it was decided to prepare dogs with artificially created defects and follow their courses during life with periodic radiographic, electrocardiographic, and hemodynamic studies. After death, gross and microscopic pathologic studies were made.

METHODS

Adult mongrel dogs weighing between 10 and 20 kilograms were used. All dogs were kept under observation for 2 weeks to make certain they were in good health.

Nembutal was used as anesthesia (100 mg. per 5 pounds of body weight). Endotracheal tubes were inserted and a demand valve respirator was used with oxygen. The procedures were monitored electrocardiographically.

Intra-arterial and intracardiac pressures were determined with the Hamilton type of electromanometer, and oxygen saturations were measured with the Waters-Connelly type of cuvette oximeter. A multichannel electrocardiograph was used as the recording instrument.

Each dog had a previously prepared Van Leersum carotid loop which simply brought the carotid artery to the surface and encased it in a layer of skin. This facilitated the obtaining of intra-arterial pressures. In some dogs the apex of the heart was sutured to the chest wall so that direct left ventricular pressures could be obtained.

Base-line studies were performed on each dog before the artificially created defects were produced. These included roentgenograms of the chest, electrocardiogram, intra-

arterial pressure readings in the carotid and femoral arteries, and right heart catheterization via the jugular vein.

All major surgical procedures were performed through a left thoracotomy. The aorta-left pulmonary shunts were all of the Potts-Smith type. The size of the anastomosis varied somewhat with the size of the dog, but an effort was made to construct the shunts with a diameter of 3 and 5 mm. The coarctation was gradually produced by sleeving the aorta at the appropriate level with an Ameroid plastic ring encased in stainless steel, as originally described by Berman.[13] Fig. 1 shows a postmortem specimen of the aorta with the Ameroid ring in place. There is definite constriction of the lumen of the aorta encased by the ring; above and below the constriction it is not unusual. In the preductal coarctation, the ring was placed on the descending thoracic aorta just distal to the left subclavian artery. In the postductal coarctation the ring was placed in the middle third of the descending thoracic aorta.

After the dogs recovered from the surgical procedures the measurements mentioned under base-line studies were carried out at periodic intervals until the animal died or was sacrificed.

All animals received parenteral penicillin and streptomycin for one week postoperatively. Blood cultures and blood counts were obtained when there was evidence of infection.

The following groups of animals were prepared for study (Fig. 2):

Group I. Four adult dogs were prepared with surgically created aortic-pulmonary shunts of 4 mm. in diameter (patent ductus arteriosus).

Group II. In 4 adult dogs a slowly developing aortic constriction distal to the origin of the left subclavian artery was surgically initiated (coarctation of the aorta).

Group III. Seven adult dogs were pre-

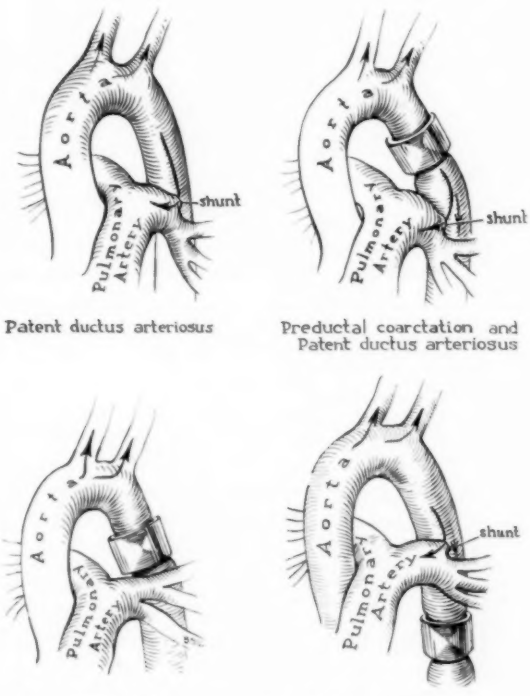

Fig. 2. The artificially created defects in the four groups of animals.

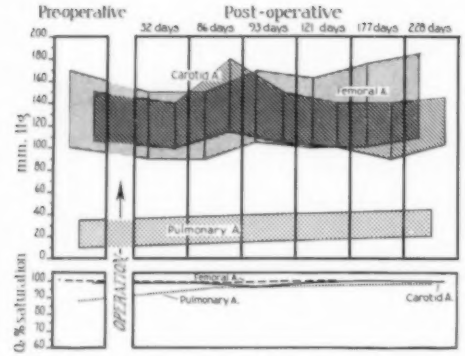

Fig. 3. Graphic course of Dog 20 with an artificially created patent ductus arteriosus. The results of catheterization are also shown in Table II. There is definite increase in arterialization of the blood in the pulmonary artery but only a mild increase in pressure. The systemic pressures show little change.

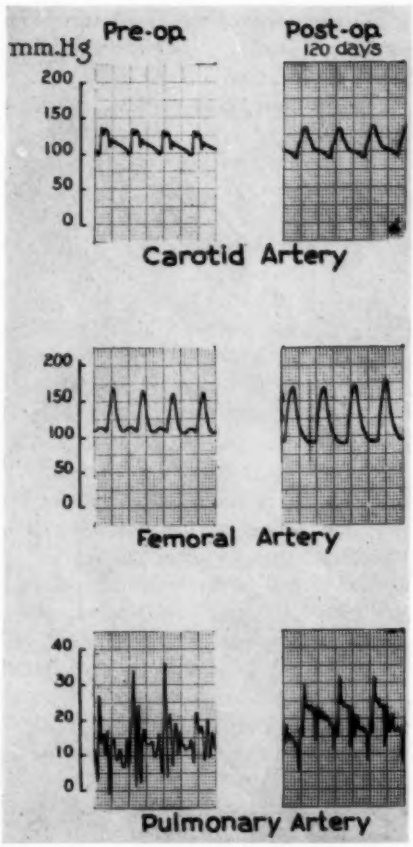

Fig. 4. Pre- and postoperative direct pressure tracings upon Dog 12 with an artificially created patent ductus arteriosus. There is a slight increase in pulse pressure in the postoperative tracings and no change in the pulmonary artery pressure.

pared with a shunt of 4 mm. in diameter between the left pulmonary artery and the aorta. Proximal to this defect a slowly developing constriction of the aorta was initiated (preductal coarctation with patent ductus arteriosus).

Group IV. Eight adult dogs were prepared with an aortic-pulmonary shunt of 3 to 4 mm. in diameter, distal to which a slowly developing constriction of the aorta was initiated (postductal coarctation with patent ductus arteriosus).

After death of the animals, autopsies were performed by one of us (F. K.) a member of the Washington University Department of Pathology.

The thoracic and abdominal contents were inspected. The size of the shunt was measured with calipers. The degree of coarctation was accurately determined with graduated cylinders so that the percentage reduction in a cross-sectional area could be calculated according to the formula noted below.* The heart and lungs were fixed in 10 per cent formaldehyde. After fixation, twelve blocks from each lobe of the lung and two of the heart were taken for paraffin or carbowax sections.[14] Selected blocks were taken for frozen sections. One half of the sections were stained with hematoxylin and eosin, and the rest with aldehyde-fuchsin-Van Gieson-iron hematoxylin (for elastic and connective tissue). The frozen and carbowax sections were stained with oil-red-O for fat. All microsections were examined particularly for the presence of organized thrombi and arteriosclerotic plaques.

*The degree of coarctation was measured by the following formula:

$$\text{Degree of coarctation} = 100 - \frac{r^2}{R^2} \times 100.$$

r = radius of the aorta at the site of coarctation.
R = radius of the aorta above the coarctation.

The circumference $= 2\pi r$. The radius can be calculated from the measured circumference. The area $= \pi r^2$ and the degree of coarctation is the ratio between the respective areas.

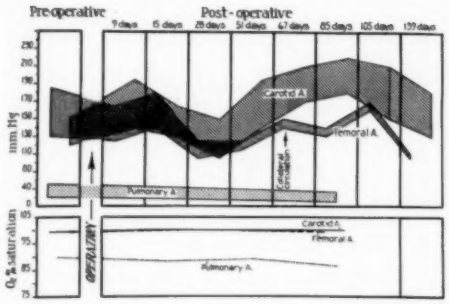

Fig. 5. Course of Dog 31 with artificially produced coarctation of the aorta. The catheterization data are taken from Table II which summarizes the findings in the other animals in this series.

RESULTS

A. Physiologic studies:

Group I (Patent ductus arteriosus). The dogs in this group were all sacrificed, 2 at 4 months, 1 at 9 months, and 1 at 10 months (Table I). These animals all had the typical continuous murmur of a patent ductus but showed no ill effects. No electrocardiographic abnormalities developed and all showed minimal cardiomegaly and pulmonary vascular engorgement on roentgenographic examination. The catheterization data showed pronounced arterialization of the blood in the pulmonary artery in all animals, thus indicating patency of the artificially created connection between the aorta and pulmonary artery. The systemic blood pressure determinations were quite variable and showed no consistent pattern. The pulmonary artery pressure in Dog 12 showed a transient rise but at the time of sacrifice the pressure was only 7 mm. Hg higher than the preoperative pressure. Dog 19 at time of death still showed a moderate elevation (18 mm. Hg) in the pulmonary artery pressure above the preoperative level. Dog 20 showed a transient rise in pressure in the pulmonary artery and Dog 39 showed no changes. Fig. 3 is a graphic representation of the course of Dog 20, illustrating the pressure determinations in the systemic and pulmonary circuits. Fig. 4 (Dog 12) shows the pre- and postoperative pressure tracings

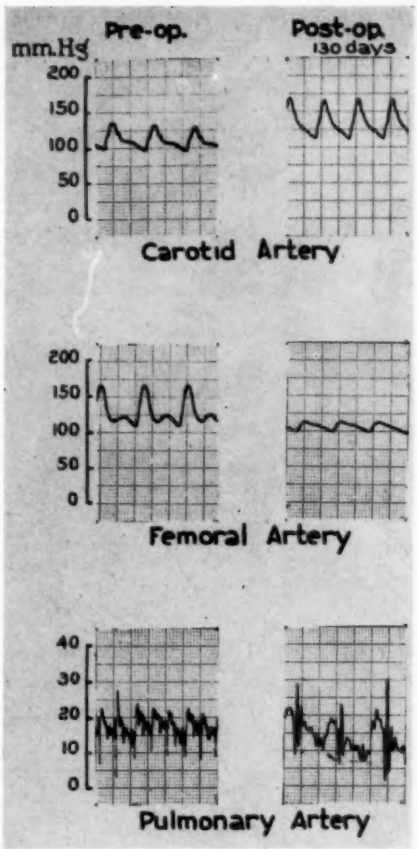

Fig. 6. Pre- and postoperative direct pressure tracings upon Dog 29 with an artificially created coarctation of the aorta. There is a moderate gradient in pressure between the carotid and femoral arteries. There is no increase in the pulmonary artery pressure.

of the systemic vessels and pulmonary artery, which indicate little change.

Group II (Coarctation of the aorta). Three dogs lived free of symptoms; 2 of these were sacrificed 5 months and one 13 months postoperatively. One dog (30) developed pulmonary edema and died 50 days after operation. All 4 of the dogs had well-localized systolic murmurs heard best on the left side of the chest. The femoral pulses became imperceptible about one month after operation, and in about 2 months the intercostal vessels became easily palpable, sug-

Table I. Group I. Patent ductus arteriosus

Dog No.	*Site*	*Preoperative*		*2 weeks*		*1 month*	
		O_2*	*P**	O_2	*P*	O_2	*P*
12	Carotid artery	102	120/105				
	Femoral artery	102	190/120				
	Pulmonary artery		28/5				
	Right ventricle						
19	Carotid artery	100	175/120	101	120/70	94	150/90
	Femoral artery	100	260/180	101	175/75	94	190/85
	Pulmonary artery	90	32/15	97	40/5		
	Right ventricle	94		70	40/0		
20	Carotid artery	98	150/105			99	140/90
	Femoral artery	100	170/100			99	150/90
	Pulmonary artery	92	32/10				
	Right ventricle		30/0				
39	Carotid artery	100	150/105				
	Femoral artery	100	165/105				
	Pulmonary artery	80	25/10				
	Right ventricle	80	30/0				

*O_2 = % oxygen saturation.

P = pressure in mm. Hg.

Table II. Group II. Coarctation of the aorta

Dog No.	*Site*	*Preoperative*		*2 weeks*		*1 month*	
		O_2*	*P**	O_2	*P*	O_2	*P*
29	Carotid artery	98	120/95		140/100		150/95
	Femoral artery	99	100/95		140/95		125/95
	Pulmonary artery	78	22/10				
30	Carotid artery	100	130/100		190/120		180/135
	Femoral artery	100	160/100		180/140		150/130
	Pulmonary artery	76	22/12				
31	Carotid artery	99	150/120		165/130		150/100
	Femoral artery	99	185/130		180/140		120/100
	Pulmonary artery	92	45/20				
42	Carotid artery	100	145/115		155/115		175/125
	Femoral artery	100	170/120		160/120		170/140
	Pulmonary artery	82	22/5				

*O_2 = % oxygen saturation.

P = pressure in mm. Hg.

gesting the development of collateral circulation. At the same time, the retinal vessels showed marked tortuosity. Chest roentgenograms showed moderate cardiomegaly. Serial electrocardiograms revealed only minimal changes which were not considered significant.

About 4 weeks after operation a gradient in blood pressure became apparent between the carotid and femoral arteries in all dogs (Table II). There was also a definite rise in systolic pressure and to a lesser degree a rise in the diastolic pressure in the carotid vessels during the study period. The systolic pressure in the femoral vessels dropped and the diastolic pressure showed a slight rise; thus, there was a definite increase in the pulse pressure in the carotid vessels (20 to 45

Postoperative								Survival time (months)	Cause of death
2 months		4 months		7 months		9-10 months			
O_2	P	O_2	P	O_2	P	O_2	P		
	145/95	100	220/130	100	175/115	101	180/120	10	Sacrificed
	220/125	100	220/140	100	200/110	101	220/115		
		76	60/35	91	36/10	101	35/15		
				(Left)					
		71	60/0	88	36/0	83	40/0		
		100	150/80						
		100	220/95					4	Sacrificed
		100	50/30						
		65	45/0						
		100	150/105	101	155/110	101	140/80	9	Sacrificed
		100	170/105	101	190/110	102	140/75		
				98	45/20	92	35/20		
				89	45/0	81	35/0		
99	150/105	100	155/90						
98	190/110	100	175/95					4	Sacrificed
99	30/5	85	28/15						
83	30/0	77	30/0						

Postoperative								Survival time (months)	Cause of death
2 months		3 months		5 months		10 months			
O_2	P	O_2	P	O_2	P	O_2	P		
100	170/100	100	195/125	99	170/115			5	Sacrificed
100	115/100	100	130/110	99	120/110				
		78	27/10	58	25/8				
	210/155								
	125/118							1.6	Died. Pulmonary edema
100	210/170		220/180	100	220/145				
100	150/140		140/130	100	150/135			5	Sacrificed
88	30/10			89	28/5				
100	220/150		220/170	100	250/200	100	210/150	13	Sacrificed
100	160/140		175/155	100	200/180	100	175/150		
84	30/12			79	23/10	90	30/10		

mm. Hg), while the pulse pressure in the femoral vessels decreased (20 to 55 mm. Hg). The changes in pressure of the carotid and femoral arteries may be seen in Fig. 5 which illustrates the course of Dog 31.

Fig. 6 (Dog 29) shows pre- and postoperative pressure tracings of the carotid and femoral vessels and the development of a definite gradient in pressure. The pressure tracings of the femoral vessel show the lag in onset of the pressure curve and the rounded peaks as described by Gupta and Wiggers.[10, 11] There was no increase in pulmonary artery pressure in this dog or the other 3 dogs in this series.

Group III (Preductal coarctation with patent ductus arteriosus). The dogs in this group began to show evidence of diminish-

Table III. Group III. Preductal coarctation with patent ductus arteriosus

Dog No.	*Site*	*Preoperative*		*1 week*		*2 weeks*		*3 weeks*		*Post*
		O_2*	P*	O_2	P	O_2	P	O_2	P	
7	Carotid artery	94	120/85	92	140/90					
	Femoral artery	94	130/85	92	160/100					
	Pulmonary artery	82	20/5							
	Right ventricle		26/0							
22	Carotid artery	98	95/56		145/50	92	220/115			
	Femoral artery	99	150/90		90/55	93	120/90			
	Pulmonary artery	82	20/5			62	50/25			
	Right ventricle	70	25/0			60	50/0			
24	Carotid artery	100	145/95					98	200/125	
	Femoral artery	100	170/120					98	115/90	
	Pulmonary artery	79	22/5					76	50/15	
	Right ventricle	79	25/0					65	50/10	
25	Carotid artery									
	Femoral artery									
	Pulmonary artery									
	Right ventricle									
26	Carotid artery	96	125/95					98	160/90	
	Femoral artery	100	165/100					98	130/90	
	Pulmonary artery	72	20/5							
	Right ventricle	70	20/0							
37	Carotid artery	98	155/110			99	150/90			
	Femoral artery	98	180/105			99	140/80			
	Pulmonary artery	75	22/12							
	Right ventricle	75	22/0							
40	Carotid artery	98	105/80					99	190/110	
	Femoral artery	99	130/85					100	90/62	
	Pulmonary artery	84	15/5					100	45/15	
	Right ventricle	86	15/0					63	45/0	

*O_2 = % oxygen saturation.
P = pressure in mm. Hg.

ing cardiac reserve approximately 2 weeks postoperatively. They developed dyspnea, tachypnea, hoarseness, tachycardia, diminished exercise tolerance, and poor appetite. The presence of moist râles in the lungs, cardiomegaly, hepatomegaly, and ascites made it evident that the dogs were in serious trouble. Terminally they developed pulmonary edema and died in 13 to 56 days after operation. Dog 25 was sacrificed after he developed quadriplegia following a retrograde angiocardiogram.

All of the animals had the typical murmur of a patent ductus arteriosus. About 2 weeks postoperatively the femoral pulsations became quite weak, and all had prominent pulsations of the intercostal vessels.

Roentgenograms of the chest revealed marked cardiomegaly, pulmonary vascular congestion, and some pleural effusion. Intravenous and retrograde angiocardiograms were taken on Dogs 7, 25, and 40, which showed a functioning left to right shunt through the artificial ductus, definite aortic coarctation, and collateral circulation (Figs. 7 and 8). The serial electrocardiographic studies showed little change.

The catheterization data (Table III) showed that 6 dogs developed pulmonary hypertension. The degree was severe (125/40 mm. Hg) in Dog 26, and during the last catheterization there was evidence of transient reversal of flow through the ductus when the dog was breathing air. Two ani-

operative								Survival time (days)	Cause of death
4 weeks		6 weeks		7 weeks		8 weeks			
O_2	P	O_2	P	O_2	P	O_2	P		
		90	200/100					47	Died. Pulmonary edema
		90	100/80						
		86	24/10						
			24/0						
								13	Died. Pulmonary edema
		94	190/110			100	220/160	56	Died. Pulmonary edema
		94	83/55			100	78/65		
		93	25/10						
		68	30/0						
98	140/100			93	240/160			45	Sacrificed
98	180/105			98	160/105				
80	25/10			81	35/20				
90	175/90			100	190/100			56	Died. Pulmonary edema
92	125/90			100	95/80				
95	50/25			100	55/35				
64	50/0			77	60/0				
99	160/100							30	Died. Pulmonary edema
99	105/80								
96	35/15								
80	30/0								
								30	Died. Pulmonary edema

mals, 22 and 40, showed moderate elevation in the pulmonary artery pressure. There was only mild elevation in pressure in Dogs 25 and 37, and Dog 24 showed a moderate elevation in pressure 3 weeks postoperatively which did not persist.

Severe hypertension with a marked increase in the pulse pressure developed in the carotid vessels, and the hypotension in the femoral artery was rather pronounced. Fig. 9 illustrates the findings in Dog 26. After 4 weeks the femoral artery pressure fell to 80 to 100 mm. Hg which is definitely lower than that observed in the dogs with coarctation alone. This confirms the observation by Gupta and Wiggers,[10, 11] who showed that the opening of a ductal shunt in the aorta distal to a coarctation reduced the femoral artery pressure to a greater extent than that in isolated aortic coarctation.

An example of the actual pressure tracings may be seen in Fig. 10. Attention is called to the late diastolic collapse of the carotid artery pressure tracing and slightly prolonged ejection time. These changes were also described by Gupta and Wiggers[10, 11] who believed them to be due to an abnormal pattern of left ventricular discharge.

Group IV (Postductal coarctation of the aorta with patent ductus arteriosus). The 8 animals included in this study (Tables IV A and IV B) are separated into two groups, A and B. The dogs in group A (48, 53, 54,

Fig. 7. This study shows the area of coarctation with the Ameroid ring in place. There is premature opacification of the pulmonary artery indicating patency of the artificially produced ductus. The injection was made into the carotid artery with 45 c.c. of 70 per cent Urokon sodium approximately 40 days postoperatively.

Fig. 8. Demonstration of collateral circulation developed in Dog 40 four weeks after operation. The radiopaque material used was barium sulfate and the injection was made post mortem.

56) developed a pressure gradient between the carotid and femoral arteries in one month or less after operation,* whereas the dogs in group B (44, 45, 46, 49) did not demonstrate a pressure gradient until 60 days or more after operation.

The animals in this group showed essentially the same findings on auscultation as were described in Group III. The animals also developed diminished exercise tolerance but to a lesser degree than those in Group III. The dogs that died with pulmonary edema developed this terminal manifestation acutely.

The survival time in Group IV A was of the same order as in Group III, while the animals in Group IV B survived for a much longer time.

The degree of cardiomegaly and pulmonary vascular engorgement was of a moderate degree as demonstrated by roentgenograms of the chest. Three animals showed minimal electrocardiographic changes.

Dogs 49, 53, and 54 developed pressure gradients of 70 to 85 mm. Hg between the carotid and femoral arteries. The pressure gradients in Dogs 48 and 56 were small and possibly reflected a failing left ventricle. The pressure gradients in Dogs 44, 45, and 56 were slow in developing, and shortly before death the gradients were definitely less than in the animals of group A.

There was good evidence of a left to right shunt through the artificial ductus arteriosus in all animals as is shown by the marked elevation in the arterialization of the blood in the pulmonary artery.

There was no evidence of pulmonary hypertension in Groups IV A and IV B, except for Dog 44 in which there was a mod-

*The Ameroid rings were not boiled in oil (except the one used for Dog 48 which was boiled for 10 minutes) for this group of dogs; this accounted for the greater hygroscopic quality of the rings and thus a more rapid development of the coarctation. The rings used in the other experiments were boiled for approximately 30 minutes.

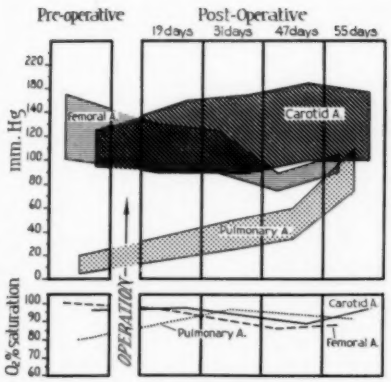

Fig. 9. Graphic course of the behavior of the blood pressures and blood oxygen saturations of Dog 26 with preductal coarctation. These studies are summarized in Table III which lists the results of studies of the other animals with these malformations. The oxygen saturation of the femoral artery is slightly lower than the oxygen saturation in the carotid vessel, thus suggesting that the blood flow might have been right to left in those instances, although the pressure in the pulmonary artery did not exceed the pressure in the aortic segment distal to the coarctation until the last catheterization study which was carried out 2 days before death.

erate rise shortly before death. There was a transient minimal elevation in pulmonary artery pressure in Dog 46. It is quite obvious, however, that the degree of rise of the right ventricular and pulmonary artery pressure was not impressive in this entire group when compared with the animals in Group III.

Fig. 11 is a graphic outline of the course of Dog 53. This may be taken as an example of the behavior of all the animals in this group. It may be seen that the pressure gradient between the carotid and femoral arteries develops early. There is also good evidence of a left to right shunt through the ductus and no evidence of right ventricular and pulmonary hypertension.

Fig. 12 shows the actual pressure tracings in Dog 49. The changes produced by the coarctation as described in the previous section, Group III, also apply to this animal. This one did not show the pulmonary hypertension demonstrated by Dog 26 (Fig. 9).

B. Pathologic Studies

The gross and microscopic anatomic findings are summarized in Table V. The artificially created shunts varied from 2 to 4 mm. in diameter. The measurements of the shunts in Group IV A were made with the organs in the fixed state and thus account for the smaller size. The measurements of the diameters above and below, as well as at the point of constriction, show that the degree of coarctation was quite marked in all dogs. Measurements of the

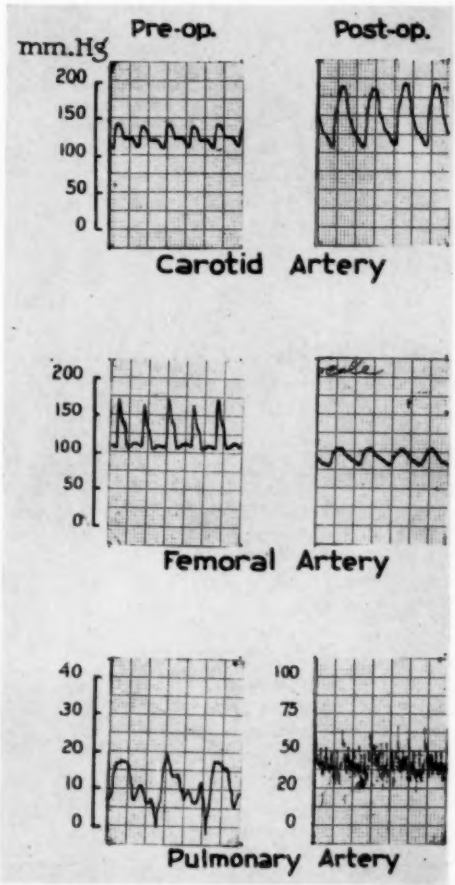

Fig. 10. Pre- and postoperative direct pressure tracings on Dog 26 with artificially created patent ductus arteriosus and preductal coarctation. There is a marked increase in pulmonary artery pressure and the expected gradient in pressure is evident between the carotid and femoral vessels.

Table IV A. Group IV A. Postductal coarctation with patent ductus arteriosus

Dog No.	*Site*	*Preoperative*		*1 week*	
		O_2*	P*	O_2	P
48	Carotid artery	100	90/75		
	Femoral artery	100	110/85		
	Pulmonary artery	68	20/5		
	Right ventricle	70	18/0		
54	Carotid artery			100	120/100
	Femoral artery	100	155/110	100	83/75
	Pulmonary artery	67	25/5	90‡	12/5
	Right ventricle	67	20/0	74	20/0
53	Carotid artery			100	150/100
	Femoral artery	100	130/95	100	155/100
	Pulmonary artery	76	20/10		
	Right ventricle	77	20/0		
56	Carotid artery			100	135/105
	Femoral artery	100	135/100	100	140/105
	Pulmonary artery	77	13/5		
	Right ventricle	74	22/0		

*O_2 = % oxygen saturation.
P = pressure in mm. Hg.
†Right pulmonary artery.
‡Left pulmonary artery.

Table IV B. Group IV B. Postductal coarctation with patent ductus arteriosus

Dog No.	*Site*	*Preoperative*		*1 month*		*2 months*		*3 months*	*Post*
		O_2*	P*	O_2	P	O_2	P	O_2	P
49	Carotid artery	100	130/110	100	175/125			100	180/135
	Femoral artery	100	210/125	100	155/120			100	150/135
	Pulmonary artery	80†	18/5	81‡	20/5			95†	15/6
	Right ventricle	80	20/0	76	20/0			84	20/0
44	Carotid artery	100	115/95	100	165/75	100	170/85		
	Femoral artery	100	145/105	100	120/60	100	145/85		
	Pulmonary artery	83	12/5			90‡	40/12		
	Right ventricle	85	17/0			79	40/0		
45	Carotid artery	98	160/130	98	150/95	99	160/85	100	185/110
	Femoral artery	98	190/130	98	175/105	99	155/100	100	160/110
	Pulmonary artery	79§	18/7	98	25/7			93‡	30/15
	Right ventricle	78	20/0	77	25/0			77	30/0
46	Carotid artery	98	140/105	100	180/105	100	200/125		
	Femoral artery	98	165/100	100	155/100	100	160/110		
	Pulmonary artery	86§	30/10			98§	40/25		
	Right ventricle	86	30/0			88	40/0		

*O_2 = % oxygen saturation.
P = pressure in mm. Hg.
†Left pulmonary artery.
‡Right pulmonary artery.
§Main pulmonary artery.

Postoperative						Survival time (days)	Cause of death
2 weeks		3 weeks		4 weeks			
O_2	P	O_2	P	O_2	P		
99	90/63	99	92/67		110/75	43	Died. Pulmonary edema
98	120/75	99	98/65		100/75		
		99	20/7†				
		65	15/0				
100	120/85	100	165/105			24	Died. Rupture of aorta
100	70/65	100	80/75				
92‡	30/15	87‡	20/10				
68	30/3	76	22/0				
	160/100		250/160	98	160/108	31	Died. Pulmonary edema
	125/90		210/70	98	88/78		
92	25/10			87†	25/10		
				93‡			
90	30/0			70	27/0		
100	140/100					17	Died. Pulmonary edema
100	125/95						
92‡	22/10						
79	15/0						

operative								Survival time (months)	Cause of death
4 months		6 months		8-9 months		10-11 months			
O_2	P	O_2	P	O_2	P	O_2	P		
			210/150					7	Sacrificed
			135/125						
100	150/95			100	175/100			9⅔	Died. Pulmonary edema
100	150/100			100	155/105				
100§	40/15			100	40/20				
85	50/0			79	45/0				
100	200/130			100	160/100	99	145/85	11	Died. Pulmonary edema
100	175/125			100	120/85	99	96/76		
91‡	25/10			100†	25/5	99†	20/8		
79	25/0			70	20/0	74	20/0		
100	200/125			100	200/90	100	210/135	12	Sacrificed
97	175/125			100	160/120	100	165/155		
100†	20/10			100†	40/20	100†	26/16		
80				81	40/0	65	26/0		

Table V. Pathologic features

Group	*Dog no.*	*Survival*	*Cause of death*	*Diameter of aorta (mm.)*			*Degree of coarctation (%)*
				Above coarctation	*At coarctation*	*Below coarctation*	
I. Patent ductus arteriosus	12	5 months	Sacrificed				
	19	1.6 months	Sacrificed				
	20	5 months	Sacrificed				
	39	13 months	Sacrificed				
II. Coarctation of the aorta	29	10 months	Sacrificed				95
	30	4 months	Died. Pulmonary edema	12	3	10	94
	31	9 months	Sacrificed	9	0	6	100
	42	4 months	Sacrificed	10	0	7	100
III. Preductal coarctation of the aorta with patent ductus arteriosus	7†	7 days	Died. Pulmonary edema	10	5	8	76
	22	13 days	Died. Pulmonary edema	10	5		75
	24	56 days	Died. Pulmonary edema	13	3	9	95
	25	45 days	Sacrificed	9	5		70
	26	56 days	Died. Pulmonary edema	10	3		91
	37	30 days	Died. Pulmonary edema	10	4.5	7	80
	40	30 days	Died. Pulmonary edema	9	3	6	89
IV A. Postductal coarctation of the aorta with patent ductus arteriosus	48	43 days	Died. Pulmonary edema	10	2.5	8.5	94
	54§	24 days	Died. Rupture of aorta	12	2	10	97
	53§	31 days	Died. Pulmonary edema	9	4	6	80
	56§	17 days	Died. Pulmonary edema	9	4		80
IV B	49	7 months	Sacrificed	9	3	8	89
	44	9⅔ months	Died. Pulmonary edema	8	3	9	86
	45	11 months	Died. Pulmonary edema	8	5		63
	46	12 months	Sacrificed	9	3	7	89

*F.I.T. = Fibrous intimal thickening.

†In one dog (No. 7) necrosis, characterized by a mononuclear reaction, involved a part of one small artery. This lesion occurred in a dog the pulmonary artery pressure of which, when measured 45 days postoperatively, was not significantly greater than it was before operation. Since the necrotic vessel was in an animal with multiple thrombi and infarcts, it is possible that the arteritis and necrosis were a result of thromboembolism.

thickness of the right and left ventricular muscle walls are also recorded. An accurate assessment of cardiac hypertrophy could not be made in this study. Pertinent changes were not seen in other organs except in the lungs.

The lungs of most animals of all groups were moderately to markedly congested and edematous without demonstrable relation to the type of defect. Pulmonary infection was infrequently seen, and only as acute bronchitis without pneumonia.

Pulmonary infarcts of variable size (usually small, but involving an entire lobe in one animal, Dog 40) were found in 6 dogs which had combined defects (Dogs 40, 44, 48, 53, 56, 71). Pulmonary thrombi (Figs. 13, 14) in various stages of organization were found in 5 of these dogs (all except 53) either at the site of sutures in the pulmonary artery or distally. Occasional small organizing pulmonary thrombi were found in 5 additional animals (26, 29, 30, 45, 46). One small pulmonary thrombus was found in each of 2 dogs with coarctation (Nos. 24 and 30) and in none with only a shunt. With the exception of Dog 40, the thrombi did not appear to involve a sufficient segment of the pulmonary vasculature to have been responsible for any important functional disturbance.

Eccentric or concentric fibrous intimal lesions (Fig. 15) characteristic of arteriosclerosis of small pulmonary arteries were

Size of shunt (mm.)	Thickness of ventricle (mm.)		Collateral circulation (+)	Pulmonary changes				
				Number of pulmonary arteries showing		Number of infarcts in entire lungs	Congestion and edema	Number of vessels with arteritis
	Right	Left		F.I.T.*	Thrombi			
½	5	17		0	0	0	Slight	0
½	4	13		1	0	0	Marked	0
½	3.5	12		2	0	0	Moderate	0
½	3	12		1	0	0	None	0
	4	14	4	20	1	0	Slight	0
			2	1	1	0	Marked	0
	4	20	4	0	0	0	Marked	0
	4	16	4	0	0	0	Moderate	0
3				0	12	12	Moderate	1
5	5	20		1	0	0	Moderate	0
5	4	18	4	1	0	0	Slight	0
5	3	9	2	0	0	0	Slight	0
4	3	10	2	0	1	0	Slight	0
4	3	15	2	0	0	0	Marked	0
5	5	18	2	1	1 large to upper lobe	Entire upper lobe	Slight	0
2‡	6	14	2	9	2	2	Marked	0
2‡	7	16	2	0	0	0	Marked	0
2‡	6	14	2	1	0	1	None	0
2‡				0	2	2	Slight	0
2	5	15	2					
4	7	13	3	3	1	1	Marked	0
3	6	12	3	2	1	0	Moderate	0
3	4	13	3	2	1	0		0

‡Measured in fixed state.

§The Ameroid rings in these 3 dogs were not boiled in oil as was done in all other experiments and as described by Berman. This would account for the rapid development of the coarctation.

found in 5 of the 8 dogs with single defects (Groups I and II), and in 8 of the 14 dogs with combined defects (Groups III and IV). Seven of the 13 animals with arteriosclerotic lesions had clearly recognizable thrombi elsewhere in the lungs. The arteriosclerotic lesions consisted principally of fibroblasts and sparse collagen. Most of the lesions were found in the paraffin sections; material for histochemical tests of stainable fat was not available. Carbowax sections were used late in the study, but fat was not demonstrated in the few lesions so examined.

As indicated in Table V, lesions of any kind were uncommon in the pulmonary arteries. At least 99 per cent of the pulmonary vessels examined were free of lesions.

DISCUSSION

The data presented point out rather striking differences in the four groups of animals. There is little doubt that the dogs with coarctation and a shunt develop cardiac and respiratory difficulties shortly after the defects are produced and do not survive much more than 40 to 60 days after operation. This observation parallels our experiences with infants who are born with this combination of defects since they, too, develop congestive failure in the first 1 to 2 months of life. By contrast the animals in Groups I and II did not get into any diffi-

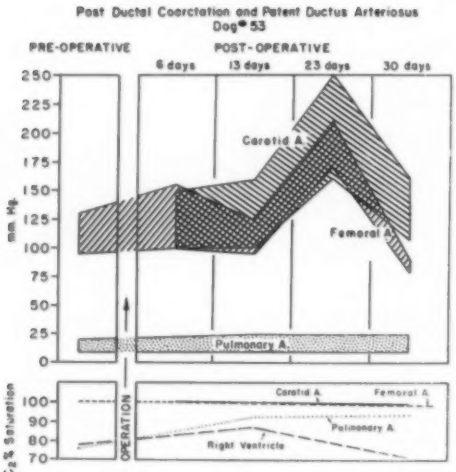

Fig. 11. Graphic course of the behavior of the pressures and oxygen saturations in Dog 53. The catheterization results are given in Table IV A which summarizes the results of catheterization of this entire group of animals.

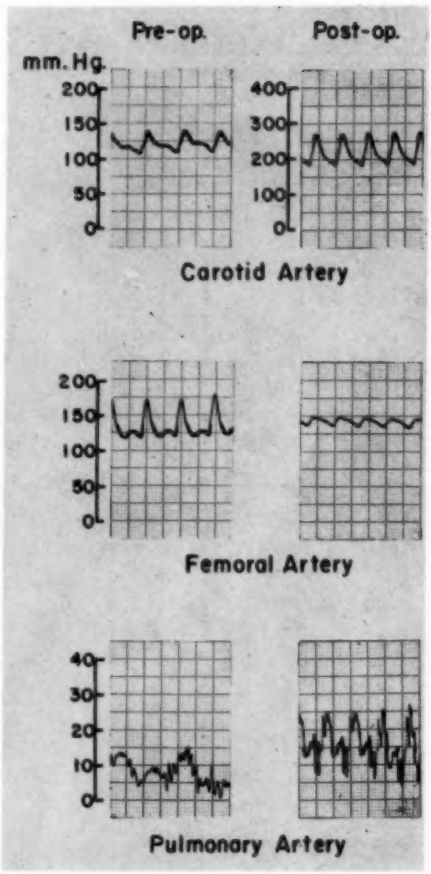

Fig. 12. Pre- and postoperative direct pressure tracings upon Dog 49 with an artificially created patent ductus arteriosus and postductal coarctation. There is a marked gradient in pressure between the carotid and femoral vessels and a moderate increase in pulmonary artery pressure.

culty during the period of observation. This, too, is in line with experiences in humans, for it is unusual for children who have either a patent ductus arteriosus or coarctation of the aorta as an isolated defect to develop congestive failure because of it.

It is important to note that the dogs with preductal coarctation and patent ductus arteriosus also developed significant pulmonary hypertension. In one dog (No. 26) the hypertension was extreme (125 mm. Hg) and during the last catheterization, while the dog was breathing air, there was evidence that the flow through the artificial ductus was right to left since the oxygen saturation was lower in the femoral than in the carotid artery. This observation was made by Gupta and Wiggers[10, 11] in their acute experiments. They state that the aortic constriction had to be over 95 per cent before the flow through the ductus reversed and became right to left. There have been similar observations in humans with similar congenital malformations.[2, 4]

The cause of the pulmonary hypertension which has been observed in infants with the combined defects and the animals in these experiments remains obscure. In infants who die with coarctation of the aorta and patent ductus arteriosus, exaggerated intimal changes of the pulmonary arterioles have been described,[1, 2, 9, 14] and in some retention of the fetal type of pulmonary vasculature has been observed. There is, of course, no easy explanation for these anatomic changes. The experiments reported here do not clarify this problem. Although pulmonary hypertension developed to a slight degree in the animals with patent ductus arteriosus and to a marked

degree in the dogs with preductal coarctation, the pathologic changes in the pulmonary vessels were not impressive in any animal.

The few arteriosclerotic lesions observed showed no discernible relationship to the presence or degree of pulmonary hypertension. The animal (Dog 26) with the highest pulmonary artery pressure (125/40 mm. Hg) had no significant intimal lesions except one small organized thrombus. There appeared to be a fairly close association between the presence of clearly recognizable organized thrombi and the presence of lesions classified as arteriosclerosis of small pulmonary arteries. In view of this association and of previously reported work[15-17] indicating that organized thrombi can form small arteriosclerotic lesions, it seems likely that the small arteriosclerotic lesions observed were a result of organization of thrombi.

Although the animals with preductal coarctation developed pulmonary hypertension while the dogs with postductal coarctation did not, there was not a great difference in longevity between the two groups. The importance of the ductus in relation to the site of coarctation was also not answered by these experiments.

Further work is being planned in an effort to answer these questions.

CONCLUSIONS

1. The experiments described here suggest that the association of a patent ductus and coarctation of the aorta artificially produced in adult dogs will cause death in

Fig. 13. This small pulmonary vessel contains a very recent fibrin thrombus. This finding, like all of the others shown, was infrequently seen. (Hematoxylin-eosin stain. ×200; reduced approximately ⅙.)

Fig. 14. Attached organizing thrombi in small pulmonary arteries such as this were occasionally found in dogs of all groups studied; it is thought that they are as likely to be related to the surgical procedure as to hypertension. (Aldehyde-fuchsin stain. ×400; reduced approximately ⅙.)

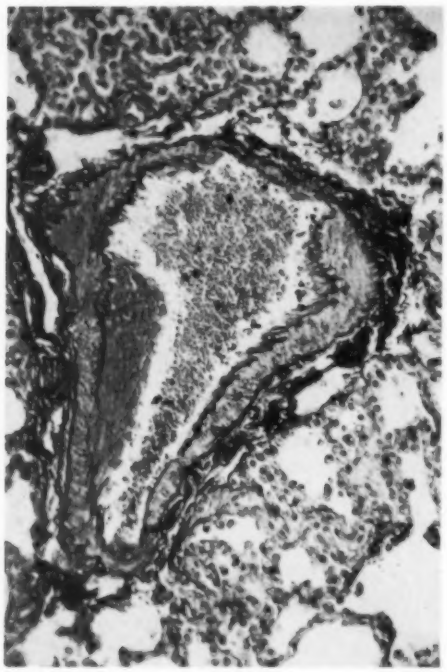

Fig. 15. Fibrous intimal thickening was an isolated finding in a very few vessels in some dogs of all groups as well as in association with thrombi and infarcts (see Table V.) It is felt that such changes are more likely the result of organization of thrombi, without demonstrable relationship to pulmonary hypertension. (Aldehyde-fuchsin stain. ×200; reduced ⅕.)

30 to 60 days. In contrast, these defects, when present alone, were compatible with life and produced little difficulty during the period of observation.

2. There was suggestive evidence that the position of the ductus in relation to the site of the coarctation made some difference in the development of pulmonary hypertension. The animals with preductal coarctation developed pulmonary hypertension whereas the animals in Group IV A with postductal coarctation did not. The period of survival was, however, essentially the same in Groups III and IV A. The animals in Group IV B did not develop pulmonary hypertension and survived for a much longer period probably because of the more slowly developing coarctation.

3. The gross and microscopic pathologic changes in the pulmonary vessels were quite minimal and certainly did not explain the development of pulmonary hypertension in the animals of Group III (preductal coarctation).

4. The observations made in these studies parallel clinical experiences in infants and support our preference for early and even emergency surgical correction as a life-saving measure when coarctation of the aorta and patent ductus arteriosus are both present.

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REFERENCES

1. Goldring, D., Behrer, M. R., Thomas, W. A., McCoy, E., and O'Neal, R. M.: Clinical and Pathological Observation in Infants With Coarctation of the Aorta and Patent Ductus Arteriosus, J. Pediat. **51:** 18, 1957.
2. Seaman, W. B., and Goldring, D.: Coarctation of the Aorta With Patent Ductus Arteriosus, J. Pediat. **47:** 588, 1955.
3. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart Disease in Infancy, New York, 1958, The Macmillan Company.
4. Cooley, J. C., Kirklin, J. W., Clagett, O. T., DuShane, J. D., Burchell, H. B., and Wood, E. H.: Coarctation of the Aorta Associated With Patent Ductus Arteriosus, Circulation **13:** 843, 1956.
5. Mustard, W. T., Rowe, R. D., Keith, J. D., and Sirek, A.: Coarctation of the Aorta With Special Reference to the First Year of Life, Ann. Surg. **141:** 429, 1955.
6. Martensen, J. D., Cutler, P. R., Rumel, W. R., and Veasy, L. G.: Management of Coactation of the Aorta in Infancy, J. Thoracic Surg. **37:** 502, 1959.
7. Behrer, M. R., Peterson, F. D., and Goldring, D.: (To be published.)
8. Calodney, M. M., and Carson, M. J.: Coarctation of the Aorta in Early Infancy, J. Pediat. **37:** 46, 1950.
9. Edwards, J. E., Douglas, J. M., Burchell, H. B., and Christensen, N. A.: Pathology of the Intrapulmonary Arteries and Arterioles in Coarctation of the Aorta Associated With Patent Ductus Arteriosus, Am. Heart J. **38:** 205, 1949.
10. Gupta, T. C., and Wiggers, C. J.: Basic Hemodynamic Changes Produced by Aortic

Coarctation of Different Degrees, Circulation **3:** 17, 1951.
11. Gupta, T. C.: The Effects of Arterial and Pulmonary Shunts on the Dynamics of Aortic Coarctation, Circulation **3:** 32, 1951.
12. Groom, D., Wood, E. H., Burchell, H. B., and Parker, R. L.: The Application of an Oximeter to Diagnostic Cardiac Catheterization, Proc. Staff Meet. Mayo Clin. **23:** 601, 1948.
13. Berman, J. K., Fields, D. C., Judy, H., Mori, V., and Parker, R. J.: Gradual Vascular Occlusion, Surgery **39:** 399, 1956.
14. Jones, R. M., Thomas, W. A., and O'Neal, R. M.: Embedding of Tissues in Carbowax, Am. J. Clin. Path. **31:** 453, 1959.
15. O'Neal, R. M., and Thomas, W. A.: The Role of Pulmonary Hypertension and Thromboembolism in the Production of Pulmonary Arteriosclerosis, Circulation **12:** 370, 1955.
16. Thomas, W. A., O'Neal, R. M., and Lee, K. T.: Experimental Pulmonary Hypertension and Arteriosclerosis, Arch. Path. **62:** 56, 1956.
17. Thomas, W. A., O'Neal, R. M., and Lee, K. T.: Thromboembolism, Pulmonary Arteriosclerosis, and Intermittent Fatty Meals; An Experimental Study, Arch. Path. **61:** 380, 1956.

Studies in sickle cell anemia

XVI. Sudden death during sickle cell anemia crises in young children

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THIS REPORT is a clinical analysis of 10 children who died suddenly during severe crisis. The clinical manifestations and postmortem findings will be cited and the mechanism of sudden death in uncomplicated sickle cell disease will be discussed.

Tomlinson[1] in 1945 called attention to a striking clinical picture of abdominal crises terminating fatally in patients with sickle cell anemia. After reviewing a series of 11 such patients, 10 of whom were children, he attributed the deaths to sudden massive hemolysis of sickled red blood cells, clinical shock with constricted peripheral vasculature, congested viscera, and cerebral edema. Four years later Raper[2] described sudden death resulting from multiple capillary blockage by sickled cells in 4 East African children and 1 adult.

We feel that it is timely to re-emphasize the vulnerability of the very young child with sickle cell anemia to severe crises which may terminate in early death. Six of the infants in this report were under 20 months of age at the time of their last hospitalization. The deaths of 6 children in this series were revealed during a comprehensive analysis of all children who died suddenly after admission to a large city hospital during the 10 year period from 1949 through 1958.

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CASE REPORTS

Case 1. G. T., a 16-month-old girl whose diagnosis of sickle cell anemia was made on a previous admission at the age of 9 months, became acutely ill on the day of admission. Immediately after arrival at the hospital the patient suffered a generalized convulsion which ceased soon after 60 mg. of phenobarbital sodium was given subcutaneously. The patient was strikingly pale and the skin was cold and clammy. Respirations were rapid and shallow. During a venous "cut down" for a packed red blood cell transfusion, 45 minutes after admission, the respirations ceased and could not be restored. Blood drawn for hemoglobin determination and cross-matching resembled "pink water" and contained less than 1 Gm. per cent of hemoglobin.

Necropsy revealed a striking gross picture of almost complete absence of color in any tissues except the spleen which was greatly engorged and of a dark purplish hue (Fig. 1). Microscopically, the spleen was packed with erythrocytes (Fig. 2).

The liver sinusoids were dilated and likewise filled with sickled red blood cells. Other organs were not remarkable except for capillary congestion.

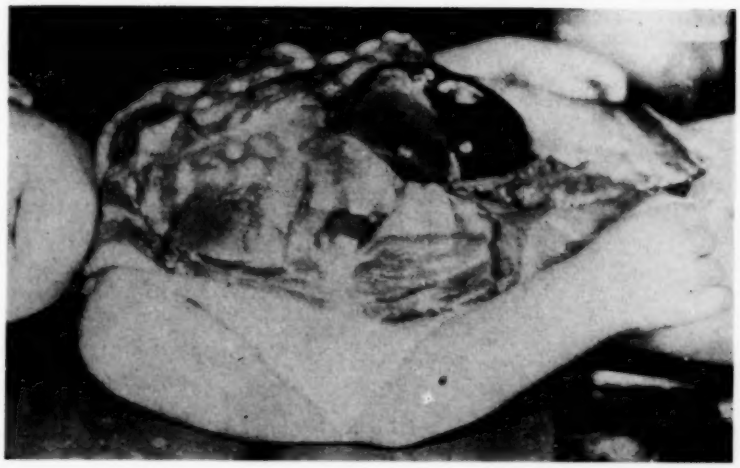

Fig. 1. Case 1. Autopsied patient demonstrating greatly enlarged spleen which weighed 274 grams (normal weight 30 grams). Note pallor of skin and other tissues.

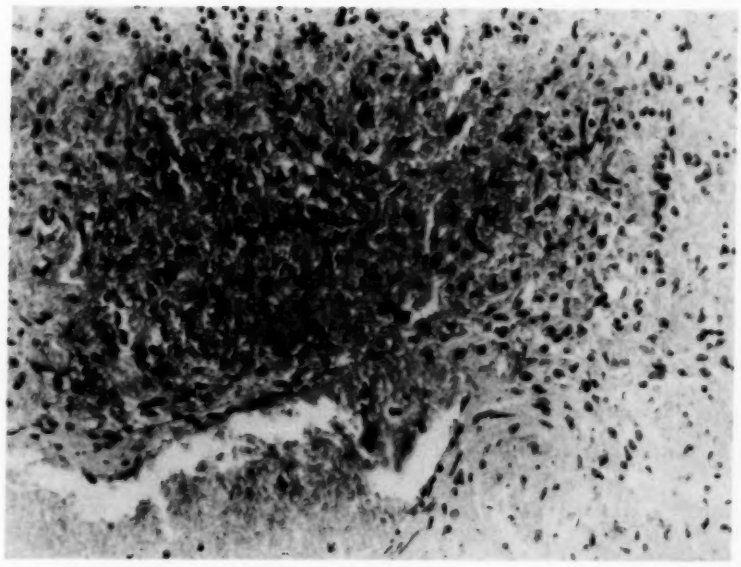

Fig. 2. Case 1. Photomicrograph of section of spleen. Note congestion and packing of splenic vessel with sickled erythrocytes. (×206; reduced ¼.)

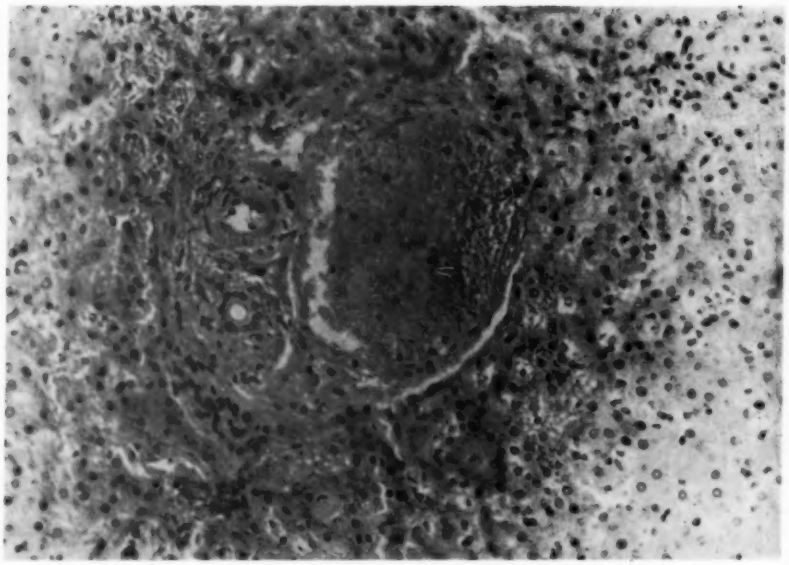

Fig. 3. Case 2. Photomicrograph of section of liver. Note packing of portal vein with sickled erythrocytes. (×206; reduced ¼.)

Case 2. J. P., a 2-year-old female with known sickle cell anemia, was seen in the emergency dispensary with a history of sudden illness, which appeared 12 hours prior to her arrival at the hospital and was characterized by a "chill" followed by one episode of vomiting. According to the mother her condition improved temporarily until about 45 minutes before admission, when she suddenly developed "breathing difficulty." The patient had had 6 previous admissions for sickle cell crises since the establishment of the initial diagnosis at the age of 2½ months.

On physical examination she was extremely lethargic. The respirations were labored and noisy. The heart rate was 180 per minute. The skin was pale but not icteric. The liver was palpable 3 cm. below the right costal margin. The posterior pharynx was hyperemic. While being examined in the emergency dispensary, the patient suddenly became more dyspneic and respirations ceased. Emergency resuscitative measures were unsuccessful.

At necropsy a markedly enlarged liver was noted and the skin was strikingly pale. The microscopic sections revealed widespread congestion of the visceral organs, particularly the liver (Fig. 3), with sickled erythrocytes. A few areas of hemorrhagic extravasation were seen in lung sections. The spleen was congested with sickled erythrocytes and pools of blood were observed in fibrosed and atrophic areas immediately about the Malpighian follicles. The kidney sections showed packing of the glomerular capillaries with erythrocytes. The bone marrow was hyperplastic and contained large numbers of nucleated red blood cells.

Case 3. W. B., an 18-month-old male, was seen for the first time after having suffered a generalized convulsion of approximately 10 minutes' duration. The patient died in the emergency room before laboratory studies could be completed. The hemoglobin concentration was less than 3 Gm. per cent. Postmortem electrophoresis revealed homozygous sickle cell hemoglobin. This was the infant's first severe illness and there had been no previous symptoms suggestive of sickle cell disease.

At autopsy the gross findings were not striking. Microscopic sections of the viscera revealed marked congestion. The liver sinus-

oids were dilated and filled with sickled red blood cells. The lungs showed edema of the alveolar spaces. Perifollicular hemorrhage was noticed in sections of spleen. The bone marrow revealed extensive erythroid hyperplasia.

Case 4. S. P., an 8-month-old male, was admitted on Oct. 31, 1954. The chief complaints were vomiting (3 or 4 times) and gasping respirations which appeared about 5 hours prior to admission. Examination revealed a temperature of 103° F., harsh pulmonary breath sounds, and markedly pale mucous membranes. Shortly after admission, while still in his mother's arms, the infant stopped breathing. Oxygen was administered immediately but he was pronounced dead 10 minutes after admission. There was a history of sickle cell anemia in 2 siblings.

At autopsy, the spleen was packed with hemolyzed erythrocytes. The liver sinusoids contained sickled forms and a small pulmonary artery was thrombosed. No other significant findings were noted.

Case 5. On Nov. 17, 1955, C. M., a 19-month-old male, was rushed to the hospital by ambulance. On arrival he was apneic and semicomatose. Upon his admission to the pediatric ward, oxygen therapy was promptly started. While an attempt was being made to secure a blood sample, respirations suddenly ceased 12 minutes after arrival at the hospital. Intracardiac Adrenalin and artificial respiration were of no avail.

Necropsy findings showed splenomegaly, massive splenic sequestration of sickled red blood cells, capillary engorgement with sickle cells involving the lungs and cerebral cortex and focal chronic interstitial myocarditis.

Case 6. L. M., a 16-month-old male, first became ill about 10 minutes after breakfast on the day of admission when he suddenly screamed, fell to the floor, and went into a stupor from which he could not be aroused.

Examination on arrival at the hospital revealed a well-developed, well-nourished male infant who was extremely pale and responded to painful stimuli with a weak cry. Respirations were 24 per minute, pulse 180 per minute. The spleen was felt 3 cm. below the left costal margin and the edge of the liver was palpable just beneath the right costal margin. The extremities were flaccid. Shortly after the patient reached the ward his respirations fell to 5 per minute and his pulse became thready. He died 17 minutes after admission. Blood which had been drawn for typing and cross matching revealed a hemoglobin of less than 2.5 Gm. per cent.

Postmortem diagnosis was sickle cell anemia with splenomegaly. The detailed necropsy report was not available for review.

Case 7. H. A., a 16-month-old male infant with known sickle cell disease, became suddenly ill on April 24, 1959, with fever, rapid respiration, and irritability. After control of a febrile convulsion which appeared 2 hours following the onset of symptoms, he was given emergency treatment for signs of pneumonia and shock but died within 3 hours of admission.

On postmortem examination the spleen was markedly enlarged and extreme pallor was noted throughout the other tissues. Microscopic examination revealed congestion of the spleen and liver with sickled cells. Other organs, particularly the lungs (Fig. 4), showed capillary congestion.

Case 8. T. K., a 4-year-old female, whose diagnosis of sickle cell anemia was established in 1945, was admitted for the fourth time on Nov. 8, 1948. Her illness was sudden and was associated with marked tachypnea. On the way to the hospital she stopped breathing, but respirations were resumed after artificial respiration was administered by her father. Physical examination showed a cyanotic, moribund, pale child with widely dilated pupils and gasping, irregular respirations. Artificial respiration was continued and oxygen administered, but death occurred shortly after admission.

Necropsy revealed hepatomegaly, splenomegaly, and marked pallor of the skin. The sclerae and mucosal surfaces were slightly icteric. Microscopic examination showed pulmonary engorgement with sickled red blood cells. The sinusoids of the liver, especially those in the peripheral portions of the

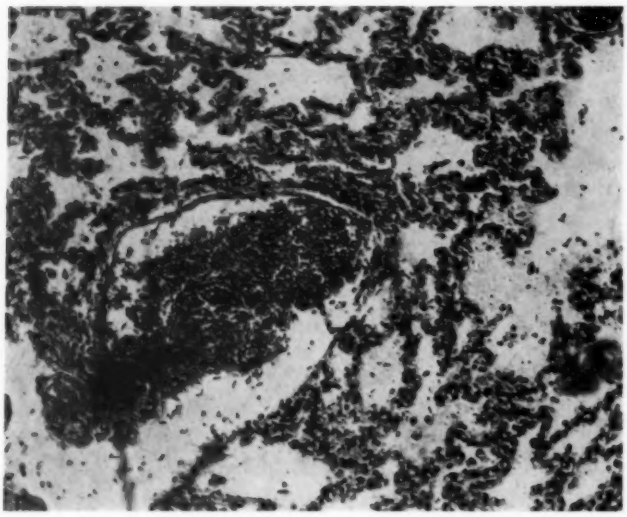

Fig. 4. Case 7. Photomicrograph of section of lung showing vascular congestion with sickled erythrocytes. (×206; reduced ⅕.)

lobules, contained pools of completely sickled red cells. These cells were also noted in the splenic follicles, the glomerular capillaries, and other small parenchymal vessels of the kidney and pancreas and in the vessels and sinuses of the lymph nodes. Sickled red blood cells with many proerythroblasts and erythroblasts were present in the bone marrow.

Case 9. C. J., a 4-year-old male, was admitted to the pediatric service on Feb. 5, 1957. The onset of his illness was acute and the presenting complaint was pain in the abdomen and back. This moribund patient was very pale, lethargic, and somewhat icteric. Fifteen minutes after admission he died.

A diagnosis of sickle cell anemia had first been made in 1954. Autopsy was not permitted.

Case 10. S. A., a 9-year-old girl with 7 previous entries for sickle cell anemia, was admitted on May 23, 1950, in a weak and lethargic state. One week prior to admission, she developed signs of an acute infection with nausea, vomiting, chills, and fever. She did not completely respond to treatment by her private physician and was noted by the parents to become increasingly pale on the day of admission. Physical examination revealed lethargy and extreme pallor. There were no obvious signs of infection. The lung fields were clear but a loud precordial systolic murmur with a suggestive gallop rhythm was heard. The liver and spleen were palpable. No abnormal neurological signs were exhibited. The red blood cell count on admission was only 730,000 with less than 2 Gm. of hemoglobin. The hematocrit was 7.

A slow transfusion of whole blood improved the patient's general condition slightly, but about 4 hours after its administration she complained of severe abdominal pain associated with rapid shallow respirations. She died shortly thereafter. Necropsy was not performed.

DISCUSSION

Death in childhood of patients with sickle cell anemia is becoming less common with better control of infectious diseases from which a number of these patients formerly succumbed. In our experience, sudden death of the type described in this report is now the most common form observed in infants and young children with this disease.

Although our series is too small for statis-

tical analysis, the clinical and necropsy findings are fairly consistent and characteristic in the 10 cases (Table I). The ages of the children ranged from 8 months to 9 years. Six infants were under 20 months of age and 9 patients were below 5 years. The patients died after brief hospitalizations of less than 24 hours; 7 children died 45 minutes or less after admission. Four of the 10 patients exhibited generalized convulsions, probably due to cerebral anoxia. The patients presented a shocklike picture of pallor, rapid shallow respirations, tachycardia, and lethargy. Six of the moribund patients died before hemoglobin determinations could be performed; the remaining 4 had extremely low concentrations (1 to 3 Gm. per cent). Two children exhibited red blood cell counts below 800,000. Only 3 patients showed clinical jaundice.

The 7 autopsies demonstrated microscopic vascular engorgement of visceral organs with sickled red blood cells. Splenomegaly was present in 6 of the 7 patients. The finding of sickled cells in the capillaries of necropsy material does not necessarily imply that the sickling represents antemortem change. The moribund condition of the patients and other evidence obtained from liver biopsies[3] suggest, however, that the change preceded death.

The pathophysiology of sickle cell anemia has been assumed to result from in vivo sickling associated with stasis of blood flow in the capillaries and venules. The vascular stasis, if prolonged, may result in thrombosis and tissue infarction. This sequence of events theoretically can occur in any organ system. A report by Kimmelstiel,[4] however, documented a case of uncomplicated sickle cell disease in which widespread foci of ischemic necrosis of the internal organs occurred without thrombotic occlusion of the arteries. He felt that peripheral vascular spasm could lead directly to ischemia of the viscera.

Sudden death in sickle cell anemia has been attributed to several causes including

Table I. Case data: Ten sudden deaths in childhood. Liver and splenic congestion was uniformly present at necropsy

Data	*Case*									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Age	17 mo.	29 mo.	18 mo.	8 mo.	19 mo.	16 mo.	16 mo.	4 yr.	4 yr.	9 yr.
Sex	F	F	M	M	M	M	M	F	M	F
Interval (hospitalization to death)	45 min.	30 min.	10 min.	10 min.	12 min.	17 min.	3 hr.	10 min.	15 min.	14 hr.
Symptoms:										
Pallor	+	+	+	+	+	+	+	+	+	+
Fever	–	–	+	+	+	+	+	–	+	–
Convulsion	+	+	+	–	–	+(?)	+	–	–	–
Lethargy	+	+	+	+	+	+	+	+	+	+
Physical Findings:										
Pallor	+	+	+	+	+	+	+	+	+	+
Splenomegaly	+	+	–	–	–	+	+	+	–	+
Hepatomegaly	+	–	–	–	+	+	+	+	–	+
Jaundice	–	–	–	–	–	–	+	+	+	–
Hemoglobin (Gm. /100 ml.)	<1		<3			<2.5				<3
Necropsy (microscopic):										
Dilated liver sinusoids	+	+	+	+	+		+	+		
Congestion of spleen	+	+	+	+	+		+	+		
Central nervous system congestion with sickle cells	–	–	–	–	+		–	–		

pulmonary fat embolism.[5-8] However, fat emboli have been seen in various organs from deaths due to other causes; therefore, definite proof of a direct causal relationship between fat emboli and death in sickle cell anemia cannot always be accepted.

Other explanations for sudden death in sickle cell anemia, such as massive cerebral thrombosis or coronary occlusion, are infrequent in childhood and are rarely reported in adults.[9] The brain and heart, however, are often sites of nonfatal but debilitating complications. Adams[10] reported a case of sudden death in a 23-year-old pregnant woman with sickle cell trait. At autopsy thrombi were seen in many cerebral vessels. Recently 3 sudden deaths of pregnant women near term with sickle cell–hemoglobin-C disease were reported from Ghana.[11] Sudden death associated with splenic engorgement and infarction has been reported in Negro soldiers with sickle cell trait during airplane flights at high altitude.[12-14]

It is possible that the spleen, liver sinusoids, and splanchnic vessels may rapidly remove intact red blood cells from the circulation under certain conditions. The patient in Case 1 is of particular interest in this connection. This infant exhibited extreme pallor of the skin and other tissues; however, at autopsy the large, dark red engorged spleen weighed 274 grams. This individual had less than 1 Gm. per cent of hemoglobin in the peripheral circulation. Although acute hemolysis was not completely ruled out, there was no evidence of clinical jaundice. When one considers the weight of this patient (9 kilograms), the extreme anemia, and the size of the spleen, it is possible to estimate arithmetically that a large portion of the total cellular volume of the blood was trapped and stagnated in the engorged splenic reservoir. Under these circumstances it is possible that death can result from peripheral shock and cerebral anoxia (convulsions). We offer this mechanism as a likely explanation for sudden death in cases of this type.

In a previous report,[15] a significant increase in the total circulating hemoglobin mass was observed to follow infusions of 6 per cent dextran in 5 per cent fructose into patients with sickle cell anemia during crises. Since no red blood cells were infused, the increase in total hemoglobin mass was explained on the basis of "mobilization" of stagnant erythrocytes from pooled reservoirs into the circulation under the dynamic stimulus of the dextran infusion. It was further postulated that the erythrocytes which were returned to the effective circulation represented cells that had been "removed by stasis" during the crisis.

Experimentally, in rats a mechanism of splenic engorgement and degorgement has been outlined by Knisely[16] (Fig. 5). This mechanism can permit the retention of large numbers of red blood cells by the splenic vascular network. MacKenzie and co-workers,[17] however, using the same methods, were unable to confirm Knisely's findings. Although a mechanism of sudden visceral congestion with cerebral anoxia and peripheral collapse seems occasionally to result in sudden death in patients with sickle cell anemia, particularly in early infancy, other factors undoubtedly contribute. Dehydration associated with vomiting or anorexia should be considered because it is easier for the thirsting

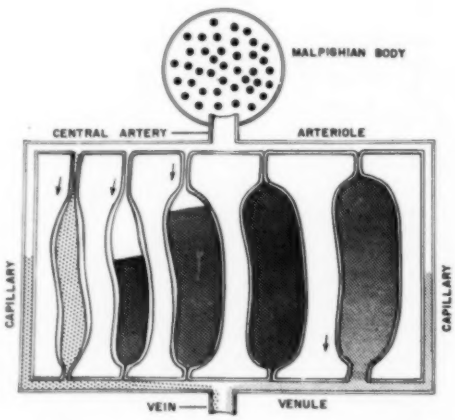

Fig. 5. Venous sinus cycle in mammalian spleen. Sinuses lie between arterioles and venules. Closure of valves at the venular side allows for damming back of erythrocytes with release upon reopening. (Modified from Knisely, M. H.: Anat. Rec. 65: 23, 1936.)

patient with sickle cell anemia to lose water in view of his known urinary concentrating defect. Anoxic stress might lead to acceleration of in vivo sickling, sludging, and a vicious cycle of additional anoxia and sickling. The role of acute infections in the precipitation or aggravation of the pathophysiology is not clear. It is worthy of note that most of the sudden deaths herein reported were associated with acute infections. In future studies on this subject, the role of viruses should also be investigated in view of recent reports of sudden death associated with viral agents.[18] Thurman and Platou have recently cited the poor prognosis for survival in patients with sickle cell anemia where the first crisis occurred during infancy.[19]

TREATMENT OF SHOCKLIKE STATE

The problem of treatment in sickle cell anemia with signs of peripheral vascular collapse and severe anemia is not necessarily different from the usual treatment of shock. Since there is severe anemia rather than hemoconcentration, an expeditious support to the failing circulation must include transfusion of red blood cells to prevent irreversible anoxic damage to vital centers. Immediate transfusion of packed red cells (3 to 5 c.c. per pound of body weight) is recommended to supply added oxygen carriers as well as to support the total blood volume. It may be necessary to give several small transfusions daily in order to control the severe anemia. Massive infusions of blood given rapidly are not without danger. Oxygen inhalation should be administered immediately. In small children and infants this can best be achieved by the use of the tent method. Antibiotics are indicated for infection.

SUMMARY

Ten cases of sudden death occurring in children with sickle cell anemia are reported. Seven of the deaths occurred within 45 minutes of hospitalization. The clinical picture common to the entire group was extreme pallor, weakness and lethargy, shocklike appearance, tachycardia, and cold clammy skin. The most striking necropsy finding in the 7 patients autopsied was congestion of the internal organs with sickled erythrocytes.

A possible mechanism of stasis of red blood cells in the spleen, liver sinusoids, and/or splanchnic capillaries with peripheral vascular collapse and cerebral anoxia is proposed to explain sudden death in infants and small children who are already debilitated by anemia, hemolysis, infection, and the like.

In order to prevent a fatal outcome it is often necessary to provide emergency measures such as immediate transfusion of whole blood or packed erythrocytes, oxygen inhalation, and antibiotics for associated infections.

We wish to thank Col. Leo J. Geppert of Walter Reed Army Hospital for permission to include Case 3 in this series. Dr. Thomas E. Reichelderfer was helpful in providing clinical material for this report. Dr. Marvin A. Jackson supplied necropsy data for some of the cases.

REFERENCES

1. Tomlinson, W. J.: Abdominal Crises in Uncomplicated Sickle Cell Anemia: A Clinico-Pathologic Study of Eleven Cases With a Suggested Explanation of Their Cause, Am. J. M. Sc. **209:** 722, 1945.
2. Raper, A. B.: Sudden Death in Sickle Cell Disease, East African M. J. **26:** 14, 1949.
3. Ferguson, A. D., and Scott, R. B.: Studies in Sickle Cell Anemia. XII. Further Studies on Hepatic Function in Sickle Cell Anemia, A. M. A. J. Dis. Child. **97:** 418, 1959.
4. Kimmelstiel, P.: Vascular Occlusion and Ischemic Infarction in Sickle Cell Disease, Am. J. M. Sc. **216:** 11, 1948.
5. Wade, L. J., and Stevenson, L. D.: Necrosis of the Bone Marrow With Fat Embolism in Sickle Cell Anemia, Am. J. Path. **17:** 47, 1941.
6. Wyatt, J. P., and Orrahood, M. D.: Massive Fat Embolism Following Marrow Infarction in Sickle Cell Anemia, A. M. A. Arch. Path. **53:** 233, 1952.
7. Evans, P. V., and Symmes, A. T.: Bone Marrow Infarction With Fat Embolism and Nephrosis in Sickle Cell Disease, J. Indiana M. A. **50:** 1101, 1957.
8. Shellery, W. M., and Curtis, E. M.: Bone Marrow and Fat Embolism in Sickle Cell Anemia and Sickle Cell–Hemoglobin-C Disease, Bull. Johns Hopkins Hosp. **103:** 8, 1958.

9. Margolies, M. P.: Sickle Cell Anemia: Composite Study and Survey, Medicine **30:** 357, 1951.
10. Adams, J. Q.: Sudden Death in Pregnancy Due to Sickle Cell Trait, South. M. J. **50:** 898, 1957.
11. Edington, G. M.: The Pathology of Sickle Cell–Hemoglobin-C Disease and Sickle Cell Anemia, J. Clin. Path. **10:** 182, 1957.
12. Henderson, A. B., and Thornell, H. E.: Observations of Effect of Lowered Oxygen Tension in Sicklemia and Sickle Cell Anemia Among Military Personnel, J. Lab. & Clin. Med. **31:** 769, 1946.
13. Sullivan, B. H.: Danger of Airplane Flight to Persons With Sicklemia, Ann. Int. Med. **32:** 338, 1950.
14. Smith, E. W., and Conley, C. L.: Sicklemia and Infarction of the Spleen During Aerial Flight: Electrophoresis of the Hemoglobin in 15 Cases, Bull. Johns Hopkins Hosp. **96:** 35, 1955.
15. Jenkins, M. E., Scott, R. B., and Ferguson, A. D.: Studies in Sickle Cell Anemia: VII. Blood Volume Relationships and the Use of a Plasma Extender in Sickle Cell Anemia, Pediatrics **18:** 239, 1956.
16. Knisely, M. H.: Spleen Studies—Microscopic Observations of Circulatory System of Living Unstimulated Mammalian Spleen, Anat. Rec. **65:** 23, 1936.
17. MacKenzie, D. W., Whipple, A. O., and Winterstriner, M. D.: Studies on the Microscopic Anatomy and Physiology of Living Transilluminated Mammalian Spleens, Am. J. Anat. **68:** 397, 1941.
18. Gold, E., Carver, D., Heineberg, H., and Adelson, L.: Viral Infection, a Possible Cause of Sudden, Unexplained Death in Infants, Proceedings of Society for Pediatric Research, Buck Hill Falls, Pa., May 8-9, 1959.
19. Thurman, W. G., and Platou, R. V.: Sickle-Cell Disease in the Young, Proceedings of Hematology (third session), Ninth International Congress of Pediatrics, Montreal, Canada, July 19-25, 1959.

Elution of anti-A and anti-B antibody from erythrocytes of incompatible newborn infants

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HEMOLYTIC disease of the newborn infant resulting from fetomaternal incompatibility with respect to blood Group A or B is most generally called to the physician's attention because an infant has developed conspicuous jaundice within the first 24 to 36 hours of life or because a level of serum bilirubin has risen to a degree greater than is considered normal or "physiologic." On the other hand, although these clinical phenomena call attention to hemolytic disease, the clinical picture is not sufficiently pathognomonic to exclude other possible causes of neonatal jaundice, and, thus, laboratory aids must be sought.

Conventional study of the hemolytic process in infants with possible hemolytic disease due to A or B incompatibility indicates that the mean concentration of hemoglobin in cord blood is lower and the average number of nucleated erythrocytes higher in incompatible than in compatible infants; on the other hand, many incompatible infants show measurements of these parameters which are well within normal values.[1, 2] Spherocytic erythrocytes which have increased osmotic fragility are present in the blood of most clinically affected infants, but these may be found in incompatible infants who remain entirely asymptomatic. These conventional studies do not establish a firm diagnosis of A or B incompatibility.

Serologic studies have shown that clinical illness from A or B incompatibility is most common in Group A or B infants of Group O mothers.[7] Generally, however, neither the type nor the level of maternal anti-A or anti-B agglutinins will sharply distinguish affected from unaffected infants. The infant's erythrocytes usually react negatively when tested in the usual manner with anti–human globulin serum (Coombs test) for coating antibody, although free antibody is sometimes demonstrated in the infant's serum. Other tests, such as the Witebsky slide test or Low's papain test, which are usually positive,[3-9] may also be positive in infants born of heterotypic pregnancies who remain without symptoms and occasionally in compatible infants.

Zuelzer and Kaplan[4] showed that the placenta of the Group O mother is generally freely permeable to her anti-A and anti-B agglutinins, inasmuch as the Group

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O infants of such mothers generally contain both anti-A and anti-B agglutinins. On the other hand, the incompatible A or B infant of such a mother generally will have absorbed out of his serum the antibody which corresponds to his own cell type; in a few instances some such antibody may remain, though in lower titer than in the compatible infant. Zuelzer and Kaplan advanced the argument that the disappearance of these antibodies is the result of their adsorption onto group specific fetal and neonatal tissues. They attempted to elute such antibodies from the cells of the incompatible newborn infant, but achieved no positive eluates. The present study explores further the question of whether helpful information may be obtained from determination of antibody eluted from infants with hemolytic disease due to A or B incompatibility, particularly with respect to whether such eluted antibody correlates with clinical disease.

METHODS

Conventional methods were used for determination of blood types and the anti–human globulin (Coombs test) reaction of the infant's cells. Eluates were prepared from erythrocytes of umbilical cord blood by a modification of Mollison's technique[10]: (1) red blood cells were washed 7 times with cold buffered saline solution; (2) elution was accomplished by heating for 20 minutes at 56° C. a 50 per cent suspension of cells in buffered saline solution. The obtaining of positive eluates was found to depend upon scrupulous attention to keeping the cells cold until the final elution at 56° C. In addition to the fact that chilled saline solution was used for preliminary washing, all manipulations were carried out in an ice bath.

The eluate was tested for hemagglutinating antibody against a 5 per cent suspension of *fresh* A_1 or B cells in a 10 per cent solution of acacia; incubation was for 30 minutes at 37° C. and was followed by centrifugation at 500 r.p.m. for one minute and reading with the aid of a hand lens. A second test for eluted antibody employed suspension of test cells in a 10 per cent solution of LePage's photoengraving glue, followed by incubation for 15 minutes at 37° C. Each eluate was tested by both techniques against Type O cells as well as A_1 or B cells.

An antiglobulin (Coombs) test was performed on all A_1 or B cells after incubation with the eluate for 20 minutes at 37° C. Infants of mothers with Rh antibodies were excluded from consideration.

RESULTS

An attempt was made to elute antibody from the erythrocytes of 104 compatible infants, 35 of whom were Group A offspring of Group A mothers. No positive eluate was obtained in any of these infants.

In 88 incompatible infants, on the other hand, 12 positive eluates were obtained (13.6 per cent). All positive eluates were demonstrated in acacia solution, and 7 of the 12 were additionally demonstrable by the anti–human globulin technique. No antibody with activity in simple saline suspension was found in any eluate.

Of the positive eluates (Table I), 10 were found in Group A infants; in 8 instances the mother was Group O and in 2 Group B. These 10 infants constitute 21 per cent of the 47 incompatible A infants. Anti-A was also eluted from an infant of Group AB whose mother belonged to Group B.

Only one of 27 incompatible Group B infants yielded a positive eluate; the mother of this infant belonged to Group O.

Attempts were made to relate the occurrence of a positive eluate with other serologic examinations and with clinical observations (Table II). In 5 infants whose cells yielded positive eluates, a search for free antibody in the serum yielded negative results. In the case of 3 of 12 infants whose cells gave a positive eluate, the cells also showed spontaneous agglutination in glue solution. On the other hand, a positive glue test was obtained with the cells of 11 incompatible infants in whom a positive eluate was not found.

Table I. Elution of homospecific antibody from red cells of incompatible infants

Infant's type	*Mother's type*	*No. tested*	*No. positive*
A	O	38	8
A	B	9	2
B	O	15	1
B	A	12	0
AB	A	10	0
AB	B	3	1

Table II. Clinical and clinicopathologic correlates of eluates

	No. of infants	*No. icteric*	*% icteric*	*Glue test positive*
Positive elutions	12	4	33	3 (25%)
Negative elutions	76	28	36	11 (15%)

The occurrence of clinical icterus was recorded for all infants on the basis of careful daily inspection, and measurements of serum bilirubin were performed where hemolytic disease was suspected. Visible jaundice occurred in only 4 of the 12 infants whose erythrocytes gave a positive eluate. In the 3 infants of these 4 in whom serial determinations of serum bilirubin level were made, the highest observed levels were 9.9 mg. per 100 ml. on the fourth day of life, 11.0 mg. per 100 ml. on the third day of life, and 21.4 mg. per 100 ml. on the fourth day of life, respectively; this last infant received an exchange transfusion.

Twenty-eight of 76 infants with negative eluates (36 per cent) manifested icterus within the first 5 days. None required therapy.

DISCUSSION

Leikin, Rheingold, and Sites[11] found evidence of hemolytic disease of the newborn in 5.6 per cent of 230 infants who were incompatible with their mothers in the ABO system. Vaughan and Brelian[12] arrived at a similar figure, though only a minority of those infants in whom they found serologic or other evidence of incompatibility displayed clinical symptoms suggestive of hemolytic disease. Their data suggest that hemolytic disease of the newborn may be discoverable in as many as 3 per cent of all infants, either as clinical icterus indistinguishable from icterus neonatorum or as a positive test of the infant's cells for spontaneous agglutination in glue solution or in acacia solution; the latter, they have inferred, most often means that the infant's cells are coated with heterospecific antibody. The presence of falsely positive reactions in glue or acacia in some compatible infants renders these tests somewhat unreliable as to significance.

The studies here reported indicate that it is possible to elute from the cells of approximately 13 per cent of incompatible newborn infants antibody which is specific for their own cells. This appears more often possible in incompatible A infants (10 of 47) than in incompatible B infants (1 of 27), but further study will be necessary to establish the significance of this trend (chi-square is 2.87 with Yates's correction). Such a demonstration of anti-A or anti-B agglutinins attached to the infant's cells has very likely the same significance as a positive Coombs test in an infant with hemolytic disease resulting from Rh incompatibility. Neither a positive Coombs test nor a positive eluate, however, can be considered to certify the presence of clinically important hemolytic disease in an icteric infant nor the probable emergence of significant illness in an infant clinically normal at the time of the positive test; clinical disease is evidently more likely in the infant with Rh incompatibility who has a positive Coombs test than in the infant with A or B incompatibility whose cells give a positive eluate.

The combination of red blood cells with antibody and the recovery of specific antibody in the eluate, though of little diagnostic help, cannot be regarded as completely innocuous. Zuelzer and Kaplan[5] demonstrated that transfused red blood cells of the infant's own type have a shorter life span in infants born of heterospecific pregnancies than in infants born of homospecific pregnancies, even when the heterospecific infant has no clinical evidence of hemolytic

disease. The presence or absence of clinical signs of disease in infants incompatible with respect to A or B must then depend upon complex factors, including both the susceptibility of the infant's erythrocytes to hemolysis and the ability of the infant's liver to convert native bilirubin to its glucuronide. No single serologic correlate of the incompatibility of the infant serves at the present time to identify or predict the infant in whom A or B incompatibility has or will have clinical importance.

SUMMARY

It was found possible to elute homospecific antibody from the red blood cells of 13 per cent of infants incompatible with their mothers with respect to Type A or B, more often where the incompatibility involved A than when it involved B. Only 4 of 12 infants in whom a positive eluate was found had clinical evidence of possible hemolytic disease due Type A or B incompatibility; one of these received an exchange transfusion. Inasmuch as the majority of infants in whom positive eluates were found had no jaundice, and since 36 per cent of 76 infants were icteric in whom no eluates were found, the ability to elute antibody from the red blood cells of the infant incompatible with his mother with respect to A or B must be concluded to be of no value in the prediction or confirmation of hemolytic disease due to A or B incompatibility.

REFERENCES

1. Hsia, D. Y., and Gellis, S. A.: Studies on Erythroblastosis Due to ABO Incompatibility, Pediatrics **13:** 503, 1954.
2. Bryce, L. M., Campbell, K., Graydon, J. J., Jakobowicz, R., and Kiel, L.: Effect of Heterospecific Pregnancy on Haemoglobin and Red Cell Levels in Newborn Infants, M. J. Australia **2:** 337, 1949.
3. Zuelzer, W. W., and Kaplan, E.: ABO Heterospecific Pregnancy and Hemolytic Disease. A Study of Normal and Pathologic Variants. I. Patterns of Maternal A and B Isoantibodies in Unselected Pregnancies, A. M. A. Am. J. Dis. Child. **88:** 158, 1954.
4. Zuelzer, W. W., and Kaplan, E.: ABO Heterospecific Pregnancy and Hemolytic Disease. II. Patterns of A and B Isoantibodies in the Cord Blood of Normal Infants, A. M. A. Am. J. Dis. Child. **88:** 179, 1954.
5. Zuelzer, W. W., and Kaplan, E.: ABO Heterospecific Pregnancy and Hemolytic Disease. III. Hematologic Findings and Erythrocyte Survival in Normal Infants, A. M. A. Am. J. Dis. Child. **88:** 307, 1954.
6. Gunson, H. H.: An Evaluation of the Immunohematological Tests Used in the Diagnosis of AB Hemolytic Disease, A. M. A. J. Dis. Child. **94:** 123, 1957.
7. Rosenfield, R. E.: A-B Hemolytic Disease of the Newborn, Analysis of 1480 Cord Blood Specimens, With Special Reference to the Direct Antiglobulin Test and to the Group O Mother, Blood **10:** 17, 1955.
8. Low, B.: A Practical Method Using Papain and Incomplete Rh Antibodies in Routine Rh Blood Grouping, Vox Sanguinis **5:** 94, 1955.
9. Turman, C., Vaughan, V. C., and Shelly, R. M.: Incidence of Hemolytic Disease of the Newborn Due to A or B Incompatibility, Am. J. Obst. & Gynec. **71:** 885, 1956.
10. Mollison, P. L.: Blood Transfusion in Clinical Medicine, Springfield, Ill., 1951, Charles C Thomas, Publisher.
11. Leikin, S. L., Rheingold, J. J., and Sites, J. G.: Frequency of ABO Erythroblastosis, Pediatrics **22:** 65, 1958.
12. Vaughan, V. C., III, and Brelian, F. B.: Neonatal Icterus, With Special Reference to A and B Incompatibility. A Paper Read Before the Section on Pediatrics, American Medical Association, New York, June 5, 1957.

The blood volume of infants

III. Alterations in the first hours after birth

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CONSPICUOUS shifts of the fluid compartment of the blood are said to occur in the newborn infant in the first hours after birth. Extrusion of plasma from intravascular to extravascular spaces is also thought to take place. This has seemed logical since the venous hematocrit tends to increase in that period of time.

In order to record the actual volumetric changes, the plasma volumes of 12 normal full-term infants were measured within an hour of birth and again at 3, 4, or 5 hours. The measurements were made in each instance by the administration of the azo dye T-1824. Plasma volumes in the 3- to 5-hour period calculated from dye-disappearance curves were in good agreement with the direct measurements. A comparison of these measured and calculated results indicates that repeated injection of T-1824 did not produce an artificial change in plasma volume. The values obtained on the second measurement are not, then, the result of artifact and are acceptable within the limits of accuracy of the technique.

The methods used for the determinations of plasma, erythrocyte, and total blood volumes and for hemoglobin concentration and venous hematocrit have been published in Part I of this study.[1]

The infant subjects were born spontaneously, without anesthesia, after uncomplicated pregnancies. The umbilical cords were clamped immediately after delivery of the buttocks.

RESULTS

The results of the individual studies are listed in Table I, and a graphic representation of average values may be found in Fig. 1.

Body temperature. Neither rise nor fall of body temperature had any apparent effect on the volumetric changes observed in the subjects. Temperatures recorded in Table I were taken per rectum.

Hemoglobin concentration and venous hematocrit. One or the other of these values decreased slightly in 5 infants, and in one of them both values decreased. The majority of these measurements, however, demonstrated an increase. The mean hemoglobin

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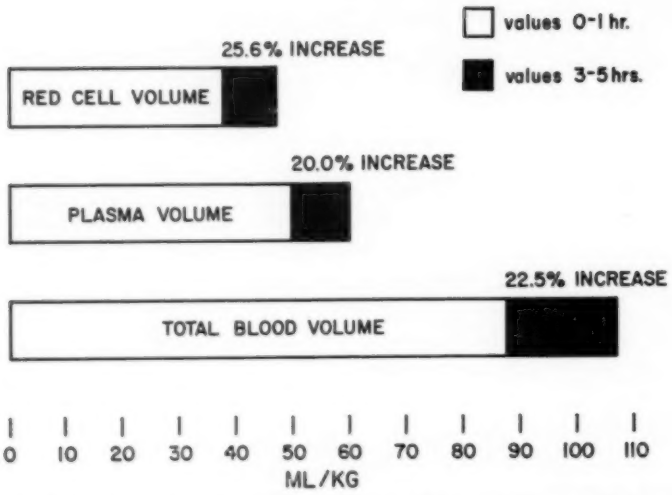

Fig. 1. The average erythrocyte, plasma, and total blood volumes of 12 normal infants at less than one hour and at 3 to 5 hours after birth are illustrated. The percentage increments during the time interval are indicated. The increase of erythrocyte volume was greater than that of the plasma volume.

concentration within one hour after birth was 16.5 Gm. per 100 ml., and between 3 and 5 hours was 16.8 Gm. per 100 ml. The mean venous hematocrit within one hour was 52.2 per cent, and between 3 and 5 hours was 53.5 per cent. The average increments were 2.4 and 2.6 per cent, respectively.

Total blood volume. The mean blood volume between birth and one hour of age was 87.9 ml. per kilogram (283 ml.), a value fairly close to that reported by Mollison[2] some years ago. The mean volume between 3 and 5 hours of age was 107.1 ml. per kilogram (345 ml.). A similar value was reported from this laboratory in another study of newborn infants 7 to 22 hours of age.[3]

The blood volume increased 22.5 per cent, or 62 ml., between one and 3 to 5 hours after birth. This represents an increment of 19.2 ml. per kilogram.

Plasma volume. The mean plasma volume between birth and one hour of life was 49.9 ml. per kilogram (160 ml). Between 3 and 5 hours of age it was 59.7 ml. per kilogram (191 ml). This was an increase of 20.0 per cent. The actual mean increment was 31 ml.; or 9.8 ml. per kilogram.

This considerable increase of plasma was 10.9 per cent of the blood volume recorded between birth and one hour of life.

Red blood cell volume. An increase in the mean red cell volume was observed which matched that of the plasma volume. The increment was 9.4 ml. per kilogram (31 ml.). The average value within an hour of birth was 37.9 ml. per kilogram (123 ml.), and between 3 and 5 hours it was 47.3 ml. per kilogram (154 ml.). This represents an average increment of 25.6 per cent, an increase nearly 6 per cent greater than that of the plasma volume.

DISCUSSION

It should be emphasized that in no instance was there a decrease in plasma, erythrocyte, or total blood volume. Expansion of the plasma and red blood cell compartments of the blood was not uniform, but was distinct and unequivocal in each infant.

The studies of Gairdner and his colleagues,[4] based on a comparison of the hemoglobin concentration and hematocrit of cord blood samples and those taken in succeeding hours after delivery, led them to conclude that a shift of plasma from the

vascular compartment occurs immediately after birth.

The findings of this investigation do not demonstrate that such a shift of fluid out of the circulatory system takes place.

That the hematocrit should have increased in the face of an undoubted expansion of the plasma volume is explained by the fact that the percentage increment of red blood cell volume was even greater.

If a transfer of plasma to extravascular spaces actually does occur, it is masked by the greatly augmented volumes demonstrated in these infants.

It seems clear that the total blood volume of the normal newborn infant should be adequate for its needs. We certainly have no reason to assume it is not. The volume of blood contained in the placenta is intended to provide for the circulation, at an effective pressure, in an organ that is amputated at birth. It is not necessarily present to augment an already sufficient volume in the fetus. We have concluded

Table I. Plasma, erythrocyte, and total blood volume values of 12 normal full-term infants within one hour, and between 3 and 5 hours after birth

Subject	*Weight (Gm.)*	*Minutes after birth*	*Body temperature (degrees centigrade)*	*Hemoglobin (Gm./100 ml.)*	*Hematocrit (%)*	*Plasma volume (ml./Kg.)*	*Blood volume (ml./Kg.)*	*Red cell volume (ml./Kg.)*
1	2,700	60	35.8	12.7	44.0	76.9	120.8	43.9
		180	35.5	13.2	43.0	84.9	131.6	46.8
2	3,800	30	36.0	19.2	65.5	45.1	98.2	53.2
		180	36.0	19.9	67.0	48.4	108.5	60.1
3	3,700	30	36.2	19.2	61.0	49.7	100.2	50.5
		180	36.3	19.4	62.0	63.1	129.4	66.3
4	3,200	42	36.4	17.0	53.0	50.8	90.3	39.6
		198	36.0	15.8	54.0	57.9	104.5	46.7
5	2,950	25	35.3	16.4	55.0	53.3	97.8	44.4
		240	35.5	18.5	60.0	58.5	116.0	57.5
6	3,670	60	34.0	18.6	52.0	40.6	71.2	30.6
		255	34.5	18.5	56.0	49.4	91.9	42.5
7	3,120	50	35.5	14.3	47.5	50.6	83.3	32.7
		230	35.7	16.6	53.0	60.3	107.3	47.0
8	3,150	60	36.2	15.0	45.0	53.7	85.5	31.8
		240	35.8	15.2	44.0	75.4	118.4	43.1
9	2,820	60	36.0	17.6	52.0	41.1	72.1	31.0
		334	36.5	15.8	48.0	57.6	95.5	37.9
10	3,250	60	34.8	15.9	53.0	39.1	69.5	30.5
		300	35.5	16.6	54.5	43.8	79.8	35.9
11	3,000	60	35.0	16.2	50.0	49.7	84.8	35.0
		300	35.3	16.3	52.0	61.0	107.0	46.0
12	3,350	50	35.4	15.4	48.0	49.2	81.6	32.4
		290	35.0	15.9	49.0	56.9	95.6	38.7
Mean (0-1 hour)	3,225			16.5	52.2	49.9	87.9	37.9
Mean (3-5 hours)	3,225			16.8	53.5	59.7	107.1	47.3
% Increase				2.4	2.6	20.0	22.5	25.6

from other studies[3-6] that if a spontaneous transfusion of placental blood takes place it does so during delivery itself and not as the result of delayed cord ligation.

It is the practice in many institutions to strip or milk the umbilical cord to produce such a transfusion. Elevation of the placenta has been shown to accomplish the same end.[7, 8]

The major purpose of inducing a placental transfusion has been to increase the hemoglobin concentration and, thus, the iron reserves of the newborn infant. If the blood volume of the infant could be increased as much as 60 ml. by a placental transfusion, an addition of only 35 to 40 mg. of iron would be gained at most. This is an amount of doubtful consequence and would be expected to have little effect on the avoidance of iron deficiency anemia in later infancy.

It seems illogical, therefore, to assume that it is a physiologic necessity to transfer the placental blood mass into a normal infant whose blood volume will increase anyway. Indeed, adverse effects of plethora in the newborn, particularly in the premature infant, have been reported,[9] and have been noted in the personal experience of many physicians.

It has been proposed that an extrusion of plasma from the pulmonary vessels to alveolar spaces may occur, contributing to the appearance of hyaline membrane disease or to other evidence of respiratory distress.[4] Such a transudation of plasma would be possible with overexpansion of the blood volume, either spontaneous or artificial. We do not know the volume of blood that must be reached before a transudation of plasma will occur. This would depend to some extent on the integrity of the vascular walls. It is possible, however, to overexpand the circulating volume of blood. In the event of anoxia or of cardiac dysfunction or of both, this would be hazardous.

The average increase in total blood volume, not based on body weight, was 62 ml. We do not know from what reservoir this volume of blood was derived. It may be supposed that it was at first sequestered in the body while adjustments from the fetal circulation took place. Reynolds[10] has shown that as the lungs expand after birth the blood flow to the head and thorax increases. Simultaneously, the blood flow to the abdominal organs and caudal end of the body decreases. Some blood is diverted to the liver, which alone might serve as a temporary depot for an appreciable quantity of blood. The vascular tissue of the expanded lungs is estimated to accommodate an increase of about 10 per cent of the blood volume.

We observed the expansion of the plasma and erythrocyte volumes after this sequence of events. It appears, then, that reservoirs are available for an amount of blood equal to the increase recorded in these infants.

The results of this investigation suggest that the time after birth at which the blood volume is measured is of considerable significance. Discrepancies in values reported by different investigators may be ascribed partly to this factor, as well as to differences in technique.

Since the values of circulating red blood cell and hemoglobin mass change so rapidly in the first hours of life, as indicated here, it becomes necessary to reassess the significance of cord blood values for hemoglobin and hematocrit and their relationship to corporeal levels.

These data represent observations of newborn infants during a sequence of events we have assumed to be normal. The results of this study indicate that great hemodynamic alterations take place with remarkable speed, even though the impetus for these adjustments may be exceedingly delicate. This conclusion leads to the supposition that pathologic variations may occur with equal speed as a result of even slight environmental change within or without the uterus.

It is entirely possible that plasma, or some components of it, could shift rapidly to extravascular spaces under conditions not observed in this study. Further investigation in this regard would be fruitful.

We regret the impossibility of measuring blood volume by simultaneous determinations of the volumes of plasma and of red blood cells. The accuracy and value of the data in this and the preceding two papers of this series would have been enhanced. The limitations imposed by the age and size of the subjects mitigated against such measurements, however. The volumetric techniques used in this study are common enough to offer comparison with other work and they have no greater disadvantages than other single methods.

SUMMARY

We have concluded that a significant increase of the circulating plasma, erythrocyte, and total blood volumes takes place in the normal newborn infant during the first few hours of life.

The average increments were: plasma volume 20.0 per cent, red blood cell mass 25.6 per cent, and total blood volume 22.5 per cent.

There was no indication that a shift of fluid, particularly of plasma, from intravascular to extravascular spaces occurred in these normal infants. This does not imply that it cannot occur, especially in the case of a circulatory overload.

Our understanding of the changes that take place in the adjustment from fetal to neonatal and then to adult circulatory and pulmonary patterns is incomplete. The results of this study indicate that caution should be used in producing an artificial expansion of the neonatal blood volume. Interference with these hemodynamic changes by effecting a transfusion of placental blood seems unwise; the hazards outweigh the rather uncertain benefits.

We have postulated that the marked increase in blood volume (62 ml. average) of the infants studied was due to an initial temporary sequestration of blood in the viscera and caudal end of the body, and that this blood was then introduced into the general circulation as vascular and pulmonary patterns were stabilized.

REFERENCES

1. Sisson, T. R. C., Lund, C. J., Whalen, L. E., and Telek, A.: The Blood Volume of Infants. I. The Full-term Infant in the First Year of Life, J. Pediat. **55:** 163, 1959.
2. Mollison, P. L., Veall, N., and Cutbush, M.: Red Cell and Plasma Volume in Newborn Infants, Arch. Dis. Childhood **25:** 242, 1950.
3. Whipple, G. N., Sisson, T. R. C., and Lund, C. J.: Delayed Ligation of the Umbilical Cord: Influence on Red Cell Volume and Hemoglobin Mass, Obst. & Gynec. **10:** 603, 1957.
4. Gairdner, D., Marks, J., Roscoe, J. D., and Brettell, R. O.: The Fluid Shift From the Vascular Compartment Immediately After Birth, Arch. Dis. Childhood **33:** 489, 1958.
5. James, L. S., Weisbrot, I. M., Prince, C. E., Holaday, D. A., and Apgar, V.: The Acid-Base Status of Human Infants in Relation to Birth Asphyxia and the Onset of Respiration, J. Pediat. **52:** 379, 1958.
6. Bernstine, J. B., and Ludmir, A.: Hemoglobin and Hematocrit Studies in the Newborn With Ligated and Non-Ligated Umbilical Cords, Am. J. Obst. & Gynec. **78:** 66, 1959.
7. Duckman, S., Merk, H., Lehman, W. X., and Regan, E.: The Importance of Gravity in Delayed Ligation of the Umbilical Cord, Am. J. Obst. & Gynec. **66:** 1214, 1953.
8. Gunther, M.: The Transfer of Blood Between Baby and Placenta in the Minutes After Birth, Lancet **1:** 1277, 1957.
9. Wood, J.: Plethora in the Newborn Infant Associated With Cyanosis and Convulsions, J. Pediat. **54:** 143, 1959.
10. Reynolds, S. R. M.: Circulatory Adaptations to Birth and Their Clinical Implications, Am. J. Obst. & Gynec. **70:** 148, 1955.

Management of the nephrotic syndrome with particular reference to the use of triamcinolone

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WITH THE TECHNICAL ASSISTANCE OF

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MUCH PROGRESS has been made in the last 10 years in the management of patients with the nephrotic syndrome. Although the etiology of childhood nephrosis is unknown and the mechanism by which adrenal steroid compounds modify nephrotic proteinuria is obscure, there is general agreement[1-4] among physicians in this field that the use of steroid therapy favorably influences the prognosis. This is not to imply that all children with the nephrotic syndrome will do well on steroid therapy or that the use of steroids decreases the need for other established principles of management. The selection of patients for treatment, the circumstances of treatment, and the long-term care continue to be important factors in achieving good results.

Satisfactory therapeutic results have been obtained in patients with the nephrotic syndrome receiving corticotropin, cortisone, hydrocortisone, and more recently the various delta-1 substituted derivatives of cortisone and hydrocortisone. The latter compounds have the advantage of less salt-retaining activity, while on a weight basis exerting more anti-inflammatory activity than the parent compounds. For the past 18 months we have used the 9-alpha-fluoro, 16-hydroxy derivative of prednisolone, triamcinolone.* This compound has been found by others[5-10] to have a comparable degree of anti-inflammatory activity and relatively little influence on water and salt metabolism. Hellman and associates[11] have shown that triamcinolone appears to be an effective steroid in the management of the nephrotic syndrome; and Lange[12] favorably reports its use as a prophylactic steroid in the long-term care of nephrotic patients.

This report concerns an evaluation of our experience in the administration of some 55 courses of triamcinolone therapy to 46 patients with the nephrotic syndrome. Nineteen

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*Triamcinolone used in these studies was supplied as Aristocort by the Lederle Laboratories Division of the American Cyanamid Company.

of these patients have had further studies of their renal status by percutaneous renal biopsy and 9 by renal hemodynamic measurements.

MATERIAL AND METHODS

The diagnosis of the nephrotic syndrome was established by a history of the insidious onset of generalized edema associated with marked proteinuria, hypoproteinemia, hyperlipemia, and the absence of evidence of reduced renal function. Recurrences of the nephrotic state were defined as the appearance of persistent proteinuria with or without edema in a patient who had been in remission following a typical episode of the nephrotic syndrome.

It seemed reasonable to assume that the effectiveness of treatment of the patient with the nephrotic syndrome would be influenced by factors in his prior status such as duration of proteinuria, response to and adequacy of earlier periods of treatment, and the presence of elevated blood pressure or altered renal function. The patients studied have therefore been divided, for the convenience of analysis, into five general classifications:

Class A: Duration less than 4 months, no prior steroid treatment, and classical findings of hypoproteinemia, hypercholesterolemia, massive proteinuria, edema, and good renal function.

Class B: Patients formerly in Class A with relapse and recurrence which is detected in less than one month. (Most of these patients were treated within 3 to 5 days after proteinuria reappeared and prior to the development of edema.)

Class C: Patients with onset of symptoms more than 4 months earlier who have not been treated or who have received treatment that is inadequate according to present criteria.

Class D: Patients who have previously failed to respond to adequate steroid therapy but who have no evidence of reduced renal function or hypertension.

Class E: Patients with hypertension and/or evidence of reduced renal function.

The status or activity of the patient's nephrotic syndrome prior to and following treatment, at the time of renal biopsy, and also at the time of renal hemodynamic studies was further graded according to the classification described by Riley[13]: (1) well; (2) proteinuria only; (3) minimal edema and proteinuria; (4) full-blown nephrotic syndrome; (5) uremia; (6) death from other causes; and (7) death in uremia.

Each patient was observed for a minimum of 3 days prior to the institution of steroid therapy and while on a standardized diet containing less than 1.0 Gm. of sodium chloride per square meter of body surface area per day. During this period blood pressure, temperature, weight, clinical status, urine volume, proteinuria, and sodium and potassium excretion were measured. Blood was obtained for the determination of sodium, potassium, chloride, blood urea nitrogen, creatinine, total serum protein, serum protein electrophoresis, cholesterol, white blood count, hemoglobin, and antistreptolysin titer. Standard methods were used for blood and urine chemical studies. Creatinine in plasma was determined by the Hare method and creatinine clearances calculated on a 24-hour basis.

Therapy with triamcinolone was begun in doses ranging from 40 to 70 mg. per square meter per day given in 4 equal doses at 6 hour intervals. The larger doses were used at the beginning of our studies; as more experience accumulated, the therapeutic dose was reduced. All patients were examined from one to three times daily by one of the authors. White blood counts were checked at 3 to 5 day intervals during treatment and blood chemistry determinations made at approximately weekly intervals.

In the presence of an intercurrent infection the triamcinolone dose was reduced to approximately twice the estimated physiologic replacement level (8 to 12 mg. per square meter per day) and intensive antibiotic therapy instituted.

Therapeutic quantities of triamcinolone were continued until the patient's urine was entirely free of protein for 2 to 3 consecutive

days or, in the presence of persistent proteinuria, for periods ranging from 22 to 28 days. When the period of intensive steroid therapy had been completed the dose of triamcinolone was then reduced in an empiric, stepwise manner at 3 to 5 day intervals by increments of 2.0 mg. per dose until a level of 2.0 mg. every 6 hours was reached, then by changing to 2.0 mg. every 8 hours, and later to 2.0 mg. every 12 hours.

Prophylactic steroid therapy was then instituted at a level of 20 to 30 mg. per square meter per day given in 3 equally spaced doses on the same 3 consecutive days of each week. This treatment was continued for 5 to 9 months beyond the last finding of proteinuria. In general, prophylactic therapy was discontinued at the beginning of the spring or summer season so as to avoid the withdrawal of treatment during that period of the year when respiratory infections are common.

The parents were instructed to examine the urine for the presence of protein each day and to report its appearance promptly. A solution of 3 per cent sulfosalicylic acid, prepared from Bumintest tablets, was used for testing at home. Positive tests for 2 or more days, even before the appearance of edema and massive proteinuria, were considered sufficient evidence of recurrence. Retreatment was then instituted, usually on an outpatient basis.

Virtual social isolation was enforced on all patients during the periods of initial and maintenance steroid therapy; specifically, the parents were asked to keep the children from birthday parties, supermarkets, indoor theaters, church, church school, and regular school for this period so as to minimize the opportunity for infections. Each patient was also maintained on 125 mg. of phenoxymethyl penicillin (penicillin V) by mouth daily for at least 1 year after the last evidence of proteinuria. Immunizing injections were not given until the patient had been entirely free of proteinuria for a period of 1½ to 2 years.

The methods used in carrying out the renal hemodynamic studies have been described previously.[14] Percutaneous renal biopsy was performed with the patient in the prone position; the Franklin modification of the Silverman needle was used.[15] Following Demerol-scopolamine analgesia (50 mg. Demerol and 0.3 mg. scopolamine per square meter), local procaine anesthesia was used. The biopsy specimens were fixed in 10 per cent buffered formol saline or Zenker's fixative and stained by routine hematoxylin and eosin, the Schiff-periodic acid technique, a silver methenamine reticulum stain, and Mallory's analine blue for examination by light microscopy.

RESULTS AND DISCUSSION

Clinical response. As might be expected, the duration of therapy was related to the time at which the patient became free of proteinuria. This in turn was directly related to the duration and severity of the nephrotic syndrome (Table I).

Class A. There were 22 patients in this classification, 13 males and 9 females. Their nephrotic syndrome was of short duration and there were no complicating factors. The average age at onset was 47 months, and the duration of active nephrosis averaged 6 weeks. The patients of Class A achieved a protein-free urine after an average of 8 days of treatment (range 5 to 12 days) on an average dose of triamcinolone of 55 mg. per square meter per day (range 45 to 67). Patients on the lower dose schedule seemed to respond as readily as those on the larger dose.

Eighteen of the patients (81 per cent) were entirely free of proteinuria at the end of the period of intensive steroid treatment while 3 still had a trace of proteinuria and one other had proteinuria plus minimal facial edema. In the follow-up period the urine of the 3 patients with traces of proteinuria cleared completely, while the patient with facial edema lost all evidence of edema but retained an intermittent trace of proteinuria. Two well patients had a recurrence of the nephrotic syndrome which was treated successfully, but both have had relapses again in recent months.

Class B. This group is composed of 7 patients (6 males and 1 female) who had been classified and treated as belonging to Class A originally but who relapsed either spontaneously or as a result of some antigenic stimulus (DPT immunization, smallpox vaccination, bee sting, or infection). The average age at onset of their nephrotic syndrome was 30 months (range 11 to 60 months). These patients showed a recurrence of nephrosis after the urine had been protein free for periods of 2 to 35 months. Pretreatment status varied from proteinuria only in 5 to proteinuria plus minimal edema in one and anasarca in one other.

The Class B patients all responded to therapy fairly promptly: they were free of proteinuria after an average of 8 days of treatment. No complications were encountered and, with the exception of one patient (No. 23) who has not returned for follow-up care, all are well at the present time.

Class C: The 8 patients with the nephrotic syndrome described in Class C presented a more difficult therapeutic problem. The disease had been present an average of 2.4 months prior to the first period of anti-inflammatory steroid therapy and an average of 10 months before the present therapy was instituted. There were 4 males and 4 females in this group; their age at onset of the nephrotic syndrome varied from 3 to 108 months (average 47 months). In general, these patients differed from those in Classes A and B in that they had not received treatment promptly following the appearance of symptoms or the treatment administered was considered inadequate by present criteria. In no case had the previous treatment eliminated all clinical and laboratory evidence of the nephrotic syndrome. Five presented with anasarca and massive proteinuria while the other 3 had proteinuria with minimal edema.

Six patients responded promptly and well to steroid therapy in an average of 8 days with the loss of proteinuria and all other clinical and laboratory evidence of the nephrotic syndrome. One other patient (No. 30) improved in that the proteinuriia decreased, as did the edema; but it was only following a prolonged period of low-dose steroid therapy that edema cleared completely, and trace amounts of proteinuria continue. Another patient (No. 35) showed no improvement in the 27 day course of steroid therapy, and the development of increasing edema plus a modest elevation in blood pressure and blood urea nitrogen led to the discontinuance of steroid therapy. He has been continued on prophylactic triamcinolonae with no complication but also with no observable improvement in his nephrotic state.

Class D. The 12 patients in Class D had also failed to respond to prior steroid therapy; but, in contrast to the subjects in Class C, these patients had received their prior steroid therapy in what is felt to be adequate and often prolonged courses. There were 8 males and 4 females in this group. The average age at onset was 50 months. These patients had been known to have the nephrotic syndrome for an average of 33 months prior to the present period of treatment—a duration that is, in general, much greater than that for the patients of Classes A, B, and C. Some of the Class D patients had received as many as 4 previous courses of corticotropin or adrenal steroid therapy; and though one earlier course may have been successful, subsequent therapy of relapses had been clearly ineffective.

These patients received an average of 27 days of intensive steroid therapy (range 8 to 35 days) before being placed on prophylactic therapy. No patient was free of proteinuria at the end of therapy, though all but 3 were free of edema. Two patients (Nos. 40 and 45) subsequently became free of proteinuria during prophylactic therapy, and the 3 (Nos. 42, 47, and 48) with minimal edema lost all traces of edema during the subsequent follow-up period.

Class E. The 4 patients in this all male group received a total of six periods of treatment. (In Table I 50 and 52 are the same patient and 51 and 53 are the same.) The nephrotic syndrome had been present for 2 to 48 months at the time of their first

Table I. Summary of the clinical status of patients with the nephrotic syndrome treated with triamcinolone

Case	Age at onset (months)	Months to		No. times previously treated	Body surface area (Sq. M.)	Daily dose steroid (mg./M²)	Days of therapy*		Status (Riley[18])†			Months followed	Mean blood pressure (mm. Hg)		Weight (Kg.)		
		First therapy	Present therapy				to protein free	total	Prior to therapy	Post therapy	Present 8/59		Control	Control (%)	Pre therapy control	Therapy control (%)	Post therapy control (%)
Class A																	
1	13	—	1	0	0.50	64	12	20	4	1	1	18	82	18‡	12.6	17	21
2	60	—	3	0	0.85	58	6	16	4	1	1	18	83	12	23.6	0	15
3	26	—	1	0	0.60	67	5	11	4	1	1	18	77	17‡	11.4	0	8
4	156	—	2	0	1.50	54	—	28	4	3	2	18	82	26‡	55.0	4	0
5	29	—	1	0	0.68	64	10	20	4	1	4	18	80	16	17.5	3	27
6	16	—	1	0	0.50	64	6	12	4	1	1	15	90	0	11.4	5	0
7	33	—	1	0	0.54	60	—	38	4	2	1	15	77	6	15.5	3	6
8	22	—	1	0	0.56	68	10	17	4	1	1	13	80	4	15	3	25
9	113	—	1	0	0.95	54	—	32	4	2	1	13	83	17‡	25	0	8
10	60	—	1	0	0.77	52	9	18	4	1	1	13	85	9	19	0	0
11	144	—	3	0	1.05	50	9	17	4	1	1	12	80	16‡	32	6	22
12	43	—	3	0	0.65	50	4	12	4	1	1	11	70	36‡	15	0	0
13	33	—	1	0	0.60	48	7	14	4	1	1	10	113	0	16	0	6
14	17	—	2	0	0.50	64	10	21	4	1	1	9	83	0	14	7	7
15	39	—	3	0	0.76	45	9	14	4	1	1	8	83	8‡	19	0	16
16	30	—	1	0	0.62	48	6	11	4	1	1	10	87	0	18	0	17
17	39	—	3	0	0.62	50	6	10	4	1	1	2	93	0	15	7	8
18	18	—	0.5	0	0.50	48	11	15	4	1	4	1	90	10‡	10	18	20
19	16	—	1	0	0.52	48	10	15	4	1	1	3	90	0	12.5	0	25
20	48	—	0.5	0	0.78	50	7	12	4	1	1	2	87	0	20.5	6	15
21	18	—	0.5	0	0.50	48	—	31	4	2	1	5	93	4	13	0	8
22	60	—	0.5	0	1.00	54	11	16	4	1	1	7	85	0	22	4	12
Av.	47		1.5		0.71	55	8	15				11	85	9	19	4	12
Class B																	
23	29	0.5	4	1	0.58	56	10	16	3	1	4	14	70	14	14.1	0	4
24	13	1	8	1	0.50	50	5	14	2	1	1	10	—	—	11	0	0
25	11	0.5	11	1	0.50	50	6	12	2	1	1	11	—	—	14	0	0
26	52	3	35	4	0.90	44	7	11	3	1	1	13	83	0	23	0	1
27	29	0.5	5	2	0.60	60	13	20	3	1	—	15	80	13	15	13	6
28	17	1	2	1	0.50	40	4	7	2	1	1	9	83	0	14	0	1
29	60	0.5	2	1	1.05	38	10	14	3	1	1	5	87	0	22	11	8
Av.	30	1	9.6		0.66	48	8	13				11	81	5	16	3.4	3

Class C																	
30	3	2	6	1	0.36	56	—	13	4	3	2	16	70	6	8	1	30
31	60	4	12	3	0.83	48	8	10	3	1	1	18	90	11	20	0	0
32	38	4	4	0	0.58	54	14	27	4	1	1	18	83	0	12	10	0
33	36	2	15	2	0.70	50	6	13	3	1	1	11	80	6	18	0	0
34	108	2	6	1	1.13	42	7	12	4	1	1	8	93	4	35	9	20
35	24	2	7	2	0.65	50	—	27	4	4	4	9	95	16‡	19	0	5
36	32	2	24	1	0.68	50	8	13	4	1	1	1	76	0	18	0	4
37	75	1	6	1	0.88	48	5	12	3	1	1	5	80	0	20	0	10
Av.	47	2.4	10	1.4	0.73	50	8	14.5				11	83	5	19	2.5	9
Class D																	
38	18	6	68	4	0.80	50	—	24	3	2	2	10	83	0	20	10	0
39	77	4	37	3	1.20	50	—	35	4	2	2	11	83	0	48	2	22
40	(37 yrs.)	7	6	1	1.50	48	—	31	4	2	1	18	83	0	60	3	13
41	18	6	60	3	0.78	55	—	22	2	2	2	18	70	2	18	0	0
42	73	2	12	3	0.90	70	—	34	4	3	2	19	97	3‡	30	7	18
43	18	5	48	4	0.77	62	—	24	4	2	2	15	103	5‡	23	0	20
44	18	7	48	3	0.75	40	—	24	4	2	2	15	82	6‡	19	5	0
45	37	4	25	3	0.76	50	—	25	4	2	1	10	88	4‡	38	9	15
46	72	6	37	4	1.25	50	—	34	3	2	2	12	82	5‡	41	7	0
47	120	6	8	2	1.20	68	—	35	3	3	2	19	82	36‡	35	0	3
48	22	1	13	2	0.55	60	—	29	4	3	2	6	83	24	13	0	8
49	73	2	16	4	1.00	32	—	8	2	2	2	4	92	10	29	0	0
Av.	49.6	4.7	31	3	0.95	53		27				13	86	8	31	3.6	8
Class E§																	
50	12	2	12	4	0.68	50	—	36	4	4	4	5	103	16	21	23	15
51	25	48	48	0	0.85	60	—	28	3	1	2	18	118‡	5‡	20	12	4
52	12	2	16	5	0.73	55	—	64	4	4	4	1	97	24	22	10	8
53	25	48	61	1	0.85	40	—	24	2	1	2	6	110‡	7‡	20	8	0
54	14	5	14	3	0.60	54	—	21	5	6	6	(D)	97‡	31‡	15	0	0
55	32	8	29	4	0.66	60	—	28	5	5	7	(D)	93‡	47‡	17	20	2
Av.	20	19	30	3	0.73	53		33				8	103	22	19	12	5

*Duration of therapy in patients whose urine did not clear of protein is omitted from determination of means in Classes A-C.

†See text for description: (1) well, (2) proteinuria only, (3) minimal edema, (4) fully developed nephrotic syndrome, (5) uremia, (6) death in uremia, (7) death from other causes.

‡These patients received reserpine either parenterally or orally when elevated blood pressure was noted.

§Nos. 50 and 52 are the same patient in separate periods of treatment. Nos. 51 and 53 are, likewise, the same patient.

steroid therapy and for 12 to 61 months prior to the present periods of triamcinolone treatment. All had a history of arterial hypertension and were receiving antihypertensive therapy in the form of either reserpine or reserpine plus a ganglion-blocking agent. Treatment was undertaken with caution; and frequent blood pressure, blood chemistry, and urine volume determinations were carried out. One patient (No. 50, 52) was treated with triamcinolone twice at intervals of 4 months for periods of 36 and 64 days, respectively. These treatments had no observable influence on the course of his severe nephrotic syndrome. Similarly, patient No. 51, 53 was treated twice in the course of the present studies at intervals of 13 months. In both instances his proteinuria disappeared during triamcinolone therapy, but following mild respiratory infections he began to show intermittent traces of protein in the urine in spite of prophylactic steroid therapy. Although response to steroid therapy was good, serial studies of renal hemodynamics (Table II) suggest a progressive loss of renal function. Patient No. 54 was unimproved on the twenty-first day of steroid treatment when he developed severe pneumonia. The dose of steroid was reduced to 10 mg. per square meter per day and intensive antibiotic therapy instituted, in spite of which he died 11 days later. Patient No. 55 tolerated steroid therapy poorly, showing a marked increase in blood pressure and ascites to the point that treatment had to be withdrawn after the twenty-eighth day. He was lost to follow-up until shortly before his death from renal insufficiency 10 months later.

Water and electrolyte excretion. In 14 cases 24 hour urine specimens were collected prior to institution of steroid therapy and throughout the period of intensive triamcinolone treatment. The dietary intake of water and salt could not be rigidly controlled; and, as the patients' appetites improved during steroid therapy, the salt intake of some increased appreciably. These data therefore varied widely and could not be considered to reflect body water and electrolyte homeostasis. The individual data are therefore omitted. In general, these studies suggested that triamcinolone, per se, in the doses used has relatively little effect upon the rates of renal excretion of water and salt in patients with the nephrotic syndrome. As would be expected, with increasing duration and severity of the nephrotic syndrome, the triamcinolone therapy was associated with more influence on urinary water and electrolyte excretion.

The 6 Class A patients showed a moderate reduction in the rate of water and electrolyte excretion prior to the time triamcinolone therapy was introduced. During the first 4 days of treatment the rate of sodium excretion was further reduced in most patients studied; however, the average daily urine volume exceeded the control value throughout the period of observation. The rate of potassium excretion was slightly increased in some and decreased in other patients. In general, the diuretic phase appeared in from 12 to 48 hours before the last traces of protein disappeared from the urine.

Water and electrolyte excretion during the triamcinolone therapy in 5 patients from Classes C and D was similar to that of the Group A patients in spite of the fact that, in general, these patients were treated for longer periods of time and the response of their proteinuria to steroid therapy was less satisfactory.

The 4 patients in Class E who were treated with triamcinolone represented too small a group to be considered critically, but generally they did not tolerate steroid therapy as well as did the patients in the other groups. They showed a tendency to retain water and sodium and demonstrated increasing potassium loss. It is possible that the reduced renal function which was shown in 3 of these patients significantly influenced renal water and electrolyte handling in the presence of steroid therapy.

Other biochemical studies. Determinations of sodium, potassium, chloride, bicarbonate, and blood urea nitrogen were carried out at 3 to 5 day intervals during treatment and showed no significant deviations from the

normal range. Total plasma protein and separation of the various protein moieties by paper electrophoresis demonstrated the characteristic marked depression of the albumin fraction and increase in the alpha$_2$ and beta globulin fractions in the untreated patients. At the completion of treatment the total and fractional protein determinations showed a return toward normal though a completely normal pattern was usually not reached for several weeks after the completion of intensive steroid therapy. Plasma total cholesterol values were elevated in all the untreated patients and gradually returned toward normal in the posttreatment period. Antistreptolysin-O titers were performed prior to steroid therapy and were all within the normal range.

Side effects. Elevation of blood pressure and excessive gains in weight were not a significant problem in patients of Classes A, B, C, and D. No symptoms attributable to the moderate increases in blood pressure were noted. The average maximum rise in blood pressure during triamcinolone therapy, expressed as a per cent of the control value, was 9 per cent for Class A, 5 per cent for Class B, 5 per cent for Class C, and 8 per cent for Class D. In some cases, however, the rise may have been obscured since reserpine, 0.25 mg. three times a day, was administered orally when moderate elevation of the blood pressure persisted. Maximum weight gain during the period of intensive steroid treatment is also expressed as percentage increase over the control weight and averaged 4 per cent for Class A, 3.4 per cent for Class B, 2.5 per cent for Class C, and 3.6 per cent for Class D.

In Class E, on the other hand, increase in mean blood pressure during steroid therapy averaged 22 per cent above the control value with a range of 5 to 47 per cent. Also, increase in weight was more marked and averaged 12 per cent above the control value with a range of 0 to 23 per cent. These findings are probably related to the pre-existing hypertension and to altered renal status.

Seven patients developed marked generalized weakness in association with prolonged intensive triamcinolone treatment. One patient in Class A (No. 7), who received a dose of 60 mg. triamcinolone per square meter per day as 8.0 mg. every 6 hours for 38 days, developed marked generalized muscular weakness on the thirty-sixth day of treatment in the absence of any reduction in the serum potassium level (K 5.2 mEq. per liter) and with no electrocardiographic evidence of hypokalemia. The weakness disappeared over a 5 day period as the steroid therapy was withdrawn. Patient No.

Table II. Studies of renal hemodynamics in relation to triamcinolone therapy of 9 patients with the nephrotic syndrome

Class and steroid treatment period No. (see Table I)	*Relation of renal study to triamcinolone therapy*	*Clinical grade at time of study*	*GFR* (c.c./min.)*	*ERPF* (c.c./min.)*	*F.F.*	*T_m PAHA* (mg./min.)*
Normal values		*1*	*50-75*	*300-450*	*.16-.24*	*35-60*
C-33	2 months after	1	94	533	0.18	31
C-34	1 week before	4	58	446	0.13	59
D-38	2 weeks before	3	78	271	0.29	28
D-39	6 weeks before	4	50	219	0 23	47
D-42	14 months after	5	79	347	0.23	—
D-43	5 months after	2	112	358	0.31	42
D-45	2 weeks before	3	82	429	0.19	27
D-46	11 months after	2	87	445	0 20	73
E-51	24 months before	3	40	275	0.14	—
E-51	11 months before	2	35	304	0.11	14
E-51	9 months after					
E-53†	2 months before	2	32	135	0.26	22

*Values corrected to 1.0 square meter of body surface area.

†Same patient as E-51.

Table III. Renal biopsy studies in patients with the nephrotic syndrome who were treated with triamcinolone

	Biopsy number and clinical circumstances at time of biopsy	*Class (Riley)*	*Description of biopsy and histologic diagnosis*
1.	Patient A-11, free of proteinuria for 6 months, on prophylactic steroids	1	Apart from some granular protein filling most glomerular-capsular spaces, no changes evident. Diagnosis: no disease found
2.	Patient A-12, free of proteinuria 1 week, therapeutic steroid dose being tapered off	1	Minimal but diffuse membranous thickening of the glomerular capillary walls. Diagnosis: membranous nephritis, mild
3.*	Patient A-14, full-blown nephrotic syndrome for 2 months, no prior treatment	4	Moderate diffuse membranous thickening of glomerular capillary walls with focal proximal and distal tubular atrophy and moderate proteinuria. Diagnosis: membranous nephritis, mild
4.*	Patient A-14, 3 weeks later and 2 weeks after proteinuria cleared following 21 days steroid therapy, dose being tapered off	1	Basement membrane thickening in most glomeruli with tubular lipiduria and proteinuria. Diagnosis: membranous nephritis, mild
5.*	Patient A-14, third biopsy, 9 months after first biopsy and 8 months after second biopsy. One brief relapse (B-27) in interim. Free of proteinuria 6½ months, on prophylactic steroids	1	Only equivocal evidence of membranous thickening of the basement membrane of the glomerular tuft. No protein in tubules. Diagnosis: membranous nephritis, minimal
6.	Patient A-17, active nephrosis for 12 weeks, no steroid therapy	4	Minimal thickening of glomerular basement membranes, otherwise normal renal architecture. Diagnosis: membranous nephritis, mild
7.	Patient A-20, active nephrosis for 12 days, no steroid therapy	4	Increase in the thickness of the glomerular basement membranes mild but generalized. No other abnormalities noted. Diagnosis: membranous nephritis, mild
8.	Patient A-21, active nephrosis for 2 weeks, no steroid therapy	4	Focal areas of thickening of the glomerular basement membranes only abnormality of renal architecture noted. Diagnosis: membranous nephritis, mild
9.	Patient A-22, active nephrosis for 3 weeks, no steroid therapy. Relapse 1 month later treated successfully with steroids (B-29)	4	Slight increase in cellularity of glomeruli with definite thickening of the glomerular basement membranes. Diagnosis: membranous nephritis, mild
10.	Patient C-33, active nephrosis 18 months and 14 months earlier, treated with steroids. Recurrence of proteinuria 3 months before, no treatment, proteinuria with minimal edema	3	Diffuse membranous thickening and lobulation of glomeruli with occasional adhesion to capsule. Diagnosis: membranous nephritis, moderate
11.	Patient C-34, on the nineteenth day of steroid treatment, free of proteinuria for 6 days. Onset 6 months earlier, one period ACTH (low dose) unsuccessful	4	Minimal thickening of glomerular basement membranes throughout, particularly at periphery of capillary loop. Diagnosis: membranous nephritis, moderate
12.	Patient C-36, active nephrosis 2 years earlier, treated partially with steroids, continuous proteinuria and intermittent edema, no prophylactic steroids in interim	4	No evidence of inflammation and architecture well preserved except for moderate increase in prominence of glomerular basement membrances. Diagnosis: membranous nephritis, moderate
13.	Patient D-38 and D-41, active nephrosis 7 years earlier, four periods of steroids, proteinuria only for the past 2 years, present therapy one month before treatment D-40 and 6 months after D-37, on prophylactic steroids	2	Diffuse membranous thickening of glomerular basement membranes with some capsular adhesions. Diagnosis: membranous nephritis, moderate

14.	Patient D-39, active nephrosis 3 years earlier, continuous proteinuria, recurrence of edema one week before biopsy, on prophylactic steroids	4	Diffuse thickening of glomerular basement membrane, particularly in hilar areas, tubules occasionally dilated and atrophic. Diagnosis: membranous nephritis, chronic
15.	Patient D-42 and D-49, active nephrosis 1½ years, proteinuria persistently but no edema for 5 months, treatment D-41 a year earlier and D-48 after biopsy	2	Diffuse alteration of glomerular structure with hyaline replacement of capillary loops and numerous capsular adhesions. Diagnosis: sclerosing glomerulonephritis, chronic
16.	Patient D-43, active nephrosis 4 years, several periods of steroid therapy, most recent 5 months earlier, proteinuria but no edema	2	Membranous thickening of all glomerular capillaries with tendency to lobulation in many. Diagnosis: membranous nephritis, chronic
17.	Patient D-44, active nephrosis for 4 years with periods free of edema but continuous proteinuria, in ninth month of prophylactic steroids after therapy	2	All but 5 of 33 glomeruli normal. Four of the latter sclerotic, one showing marked basement membrane thickening. Tubules normal. Diagnosis: localized glomerulosclerosis. No active disease identified
18.†	Patient D-45, recurrence of massive proteinuria and edema 3 weeks earlier after 10 months of trace proteinuria. Onset 2 years earlier. Still on prophylactic steroids	4	Uniform but mild thickening of glomerular basement membranes with rare capsular adhesions and occasional tendency to glomerular lobulation, some showing pericapsular fibrosis. Tubules normal. Diagnosis: membranous nephritis, moderate
19.†	Patient D-45, 8 months after previous biopsy and 7 months since last proteinuria, on prophylactic steroids	1	Comparison with the previous biopsy shows similar changes plus some sclerotic glomeruli suggesting progression or healing of inflammatory lesions. Diagnosis: membranous nephritis, chronic
20.‡	Patient D-46, active nephrosis, onset 4 years earlier, remissions with treatment until 2 years ago, continuous proteinuria and some edema since, on prophylaxis	3	Diffuse membranous thickening of all glomerular capillaries with some lobulation. Tubules dilated with protein. Diagnosis: membranolobular glomerulonephritis, moderate
21.‡	Patient D-46, 12 months after above biopsy and 11 months after steroid therapy. No proteinuria and on no therapy	2	Glomerular changes varying from mild membranous thickening to occasional glomeruli that show lobulation and atrophy. Areas of focal tubular atrophy related to mildly involved glomeruli noted. Many glomeruli virtually normal. Diagnosis: membranous nephritis, mild, with focal areas of scarring
22.	Patient E-50 and E-52, continuously active nephrosis for 18 months, several periods of treatment, all unsuccessful. On therapeutic steroids 6 weeks	5	All glomerular basement membranes thickened with occasional capsular adhesions and capsular thickening. Tubules variable, many showing vacuolization—much tubular proteinuria. Diagnosis: (1) membranous nephritis, chronic; (2) tubular changes of dextran therapy
23.	Patient E-54, postmortem specimen, last steroid therapy 11 days earlier, severe staphylococcus pneumonia, full-blown disease	6	Generalized abnormality of all glomeruli consisting of marked thickening of basement membranes and lobulation of tufts. Generalized tubular atrophy and dilatation. Diagnosis: membranolobular glomerulosclerosis, advanced
24.	Patient E-55, postmortem specimen, last steroid therapy 10 months earlier, on no therapy at time of death from renal failure	7	Generalized hyaline replacement of glomeruli with obliteration of structure. Tubules dilated and atrophic. Diagnosis: membranolobular glomerulosclerosis, advanced

*Same patient.

†Same patient.

‡Same patient.

35 in Class C also had marked generalized weakness with no electrocardiographic or chemical evidence of hypokalemia. Toward the end of the treatment period, 2 patients in Class D (Nos. 40 and 42) experienced marked generalized muscular weakness with no clinically demonstrable evidence of potassium deficit. All 4 patients in Group E showed weakness prior to beginning steroid therapy, and this seemed to be intensified in the later days of the period of therapy.

Patient No. 49 experienced a marked intensification of a preexisting behavior disturbance that made it necessary to discontinue steroid therapy. He improved rapidly but again became unmanageable when prophylactic steroid administration was attempted. No other side effects or complications attributable to triamcinolone therapy were noted.

Renal hemodynamic studies. Eleven studies of renal hemodynamics (glomerular filtration rate, effective renal plasma flow, filtration fraction, and maximum tubular excretory capacity for para-aminohippurate) were carried out in 9 of the triamcinolone-treated patients as part of another investigation (Table II).

The 2 Class C subjects (Nos. 33 and 34) had normal renal hemodynamic values and responded promptly to steroid therapy by becoming free of proteinuria. One (No. 33) was studied 2 months after successful steroid therapy while the other (No. 34) was studied the week prior to the institution of treatment with triamcinolone. Neither patient experienced a significant weight gain or elevation of blood pressure during therapy.

Of the 6 Class D patients in whom renal hemodynamic measurements were made, all but one (No. 39) had normal values for renal function and this one showed only a moderate reduction in effective renal plasma flow. These patients tolerated steroid therapy well; however, their response to treatment consistently fell short of the ideal in that, while they lost the edema, all continued to show some degree of proteinuria. Only one patient (No. 46) showed a marked increase in mean arterial blood pressure (36 per cent increase over the control value). No patient's weight increased more than 10 per cent above the pretreatment weight.

The only Class E patient (No. 51, 53) evaluated by renal hemodynamic studies was examined three times over a period of 26 months. In spite of fairly intensive antihypertensive therapy (0.5 mg. of reserpine and 50 mg. of chlorisondamine three times daily), there was a moderate increase (average of 6 per cent) in the mean blood pressure during triamcinolone therapy; and the serial renal function studies suggest that this patient is showing progressive loss of renal function.

These studies of renal hemodynamics in patients with the nephrotic syndrome suggest that steroid responsiveness cannot be reliably estimated by this method. This finding is in contrast to the recent report by McCrory[16] in which the clearance of albumin was demonstrated to correlate fairly well with response to anti-inflammatory steroid therapy. The studies also suggest that in the presence of altered renal function an elevation of blood pressure and retention of water and sodium may be anticipated in the course of steroid therapy.

Renal biopsy. The histologic data obtained by examination of percutaneous renal biopsy specimens is reported in tabular form (Table III).

The 5 untreated patients with nephrosis of short duration (Class A) showed typical, though minimal, thickening of the glomerular basement membrane without other abnormality of renal architecture. A similar change characterized the biopsy findings in 2 patients examined in the period immediately following successful steroid therapy. In 2 other patients, however, who were studied after they had been free of proteinuria for 6 months, only equivocal evidence of basement membrane thickening was found in one and the other was entirely normal.

Three patients of Class C were examined by renal biopsy. One (No. 33) had developed nephrosis 18 months earlier and subsequently experienced two relapses. Proteinuria had been present for 3 months at

the time of the biopsy, which revealed diffuse membranous thickening and a tendency to lobulation of the glomerular tuft. The second patient (No. 34), who had been known to have active nephrosis for 6 months, was studied 6 days after his urine became free of protein. The biopsy showed minimal generalized thickening of the basement membrane, particularly emphasized at the periphery of the capillary loops. Patient No. 36 had active nephrosis of 2 years' duration with a history of one brief period of steroid therapy which had not influenced the proteinuria and edema. Biopsy showed only moderate, generalized prominence of the basement membranes.

The biopsy findings in Class D patients generally suggest more significant histologic changes. Biopsy of the kidney of 5 patients with only proteinuria revealed a histologic picture varying from diffuse thickening of the basement membrane only (No. 38) to a chronic sclerosing glomerulonephritis (No. 42) with hyaline replacement of the glomerular capillary loops. Two Class D patients had a full-blown nephrotic syndrome at the time of biopsy and showed definite thickening of glomerular basement membranes, characteristic of a moderately advanced process.

One patient in Class E was examined by biopsy and 2 were studied post mortem. The biopsy specimen showed membranous thickening and capsular adhesions; the 2 post-mortem specimens revealed advanced membranolobular glomerulosclerosis.

In general, these studies suggest that patients with minimal thickening of the basement membrane may be expected to respond well to steroid therapy and that the renal histologic changes will gradually disappear if the patient remains free of proteinuria. By contrast, patients with moderate-to-advanced basement membrane changes are less likely to respond to steroid therapy by achieving a protein-free urine. Patients who show marked lobular changes with hyalinization of glomeruli are not likely to tolerate steroid therapy well and in our experience have not been significantly benefited by it.

Steroid prophylaxis. Triamcinolone as a prophylactic measure in doses of 20 to 40 mg. per square meter per day has been used in all cases on 3 consecutive days of each week. It is our impression that this treatment tends to reduce the number of relapses although alternate controls were not used and no definite data on this point are provided. No patients gave evidence of Cushing's syndrome on this interrupted

Table IV. Classification of patients with the nephrotic syndrome treated with triamcinolone

At the conclusion of intensive steroid therapy

Class	No. treated	Status at end of therapy (Riley)						
		1	*2*	*3*	*4*	*5*	*6*	*7*
A	22	18	3	1	0	0	0	0
B	7	7	0	0	0	0	0	0
C	8	6	0	1	1	0	0	0
D	12	0	9	3	0	0	0	0
E	6	2	0	0	2	1	1	0
Total all classes	55	33	12	5	3	1	1	0

At the end of a follow-up period of intermittent prophylactic therapy

Class	No. followed	Av. duration (months)	Status at end of follow-up (Riley)						
			1	*2*	*3*	*4*	*5*	*6*	*7*
A	22	11	19	1	0	2	0	0	0
B	6*	11	5	0	0	1	0	0	0
C	8	11	6	1	0	1	0	0	0
D	12	13	2	10	0	0	0	0	0
E	6	8	0	2	0	2	0	1	1
Total all classes	54	11	32	14	0	6	0	1	1

*One patient lost to follow-up.

treatment plan, and there have been no complications attributable to the use of steroid therapy in this manner.

SUMMARY

Triamcinolone in doses of 40 to 50 mg. per square meter of body surface area per day appears to be an effective agent for the treatment of the idiopathic nephrotic syndrome. The status of the treated patients at the end of intensive steroid therapy and at the conclusion of a follow-up period is summarized in Table IV. Response to treatment is more consistent in patients whose proteinuria has been present for less than 4 months at the time treatment is instituted. In certain patients wtih proteinuria of greater duration, treatment may lead to a loss of edema and reduction in the degree of proteinuria without complete clearing of the urine of protein. The significance of the persistence of modest degrees of proteinuria in relation to the ultimate prognosis can be determined only by longer periods of observation. The urine of some patients has subsequently been cleared of protein with intermittent prophylactic therapy months after intensive steroid treatment has been completed. Periods of intensive steroid therapy beyond 28 days did not appear in these studies to lead to greater improvement in the degree of proteinuria. In the doses studied, the influence of triamcinolone on water and electrolyte excretion, arterial blood pressure, and body weight was not sufficient to interrupt the treatment plan.

Prophylactic therapy in an interrupted fashion (3 consecutive days of each week) when coupled with social isolation and other anti-infection preventive measures appeared to be satisfactory in most patients in the prevention of recurrences.

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REFERENCES

1. Kohn, Jerome, L.: In Metcoff, J., editor: Proceedings of the Ninth Annual Conference on the Nephrotic Syndrome, Bethesda, Md., Oct. 24-26, 1957, p. 230.
2. Lange, K., Strang, R., Wenk, E. J., and Slobody, L. B.: The Treatment of the Nephrotic Syndrome in Children and Adults, A. M. A. Arch. Int. Med. **99:** 760, 1957.
3. Denrow, H. A.: The Nephrotic Syndrome, New England J. Med. **258:** 77, 124, 1958.
4. McCrory, W. W., and Macaulay, D.: Recent Advances in the Management of Renal Disease in Children (Part I), Pediatrics **19:** 481, 1957.
5. Hartung, E. F.: Triamcinolone in Treatment of Rheumatoid Arthritis, J. A. M. A. **167:** 973, 1958.
6. Freyberg, R. H., Bernsten, C. A., Jr., and Hellman, L.: Further Experiences with 1, 9 Alpha Fluoro, 16 Alpha Hydroxyhydrocortisone (Triamcinolone) in Treatment of Patients With Rheumatoid Arthritis, Arthritis and Rheumatism **1:** 215, 1958.
7. Kalz, F.: The Effects of Triamcinolone (Aristocort) and 6-Methylprednisolone on Some Skin Diseases, Canad. M. A. J. **79:** 400, 1958.
8. Feinberg, S. M., Feinberg, A. R., and Fisherman, E. W.: Triamcinolone (Aristocort), New Corticosteroid Hormone, Its Use in Treatment of Allergic Disease, J. A. M. A. **167:** 58, 1958.
9. Dubois, E. L.: Evaluation of Steroids in Systemic Lupus Erythematosus With Particular Emphasis on Triamcinolone and Methylprednisolone, Metabolism **7:** 509, 1958.
10. Diaz Tellechea, C. M.: Triamcinolone in the Treatment of Idiopathic Thrombopenic Purpura, Arch. med. int. **18:** 2, 1958.
11. Hellman, L., Zumoff, B., Minsky, A., Kretchmer, N., and Kramer, B.: Treatment of the Nephrotic Syndrome With Triamcinolone, Pediatrics **23:** 686, 1959.
12. Lange, K.: In Metcoff, J., editor: Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome, New York, Nov. 6-8, 1958, p. 278.
13. Riley, C. M., and Scaglione, P. R.: Current Management of Nephrosis. Statistical Evaluation and a Proposed Approach to Therapy, Pediatrics **23:** 561, 1959.
14. Daeschner, C. W., Moyer, J. H., Bell, W. R., and Clark, J. L.: Parenteral Administration of Reserpine in the Treatment of Hypertension Due to Acute and Chronic Nephritis: Clinical and Renal Hemodynamic Studies, Pediatrics **19:** 566, 1957.
15. Muehrcke, R. C., Kark, R. M., and Pirami, C. L.: Technique of Percutaneous Renal Biopsy in the Prone Position, J. Urol. **74:** 267, 1955.
16. McCrory, W. W., Rapoport, M., and Fleisher, D. S.: Estimation of Severity of the Nephrotic Syndrome in Childhood as a Guide to Therapy and Prognosis, Pediatrics **23:** 861, 1959.

The leukocyte response in patients with shigellosis

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THE use of so simple a laboratory technique as the total leukocyte count as an aid in the differential diagnosis of many diseases is well established. It is perhaps, the most commonly employed laboratory procedure and has become extremely important from a practical standpoint in the differentiation of bacterial and viral infections. In pediatric practice it is often very difficult to decide before the results of bacteriologic studies are available whether or not a child with diarrhea has a bacterial, viral, or other type of infection. In order for proper therapy to be instituted this decision is obviously of practical importance.

The purpose of this paper is to present the white blood cell counts from a group of infants and children with proved shigellosis and present some data to support a possible explanation of these findings.

MATERIALS AND METHODS

The patients included in this report are infants and children with shigellosis who were admitted to the pediatric service of the University Hospital over a 3 year period. The bacteriologic diagnosis of shigellosis was made in the standard accepted manner and has been described in detail previously.[1] The "crude endotoxin" used in the animal experiments was prepared by a method described previously[2] from an organism, *Shigella flexneri* (type 2a), isolated from a patient in this series. The material was essentially the filtered (Seitz) supernate of a ground saline suspension of washed bacterial cells grown on brain-heart-infusion agar. Leukocyte counts were done on heparinized venous blood in the conventional manner on a Spencer Bright Line counting chamber, with the use of N/10 hydrochloric acid as the diluting fluid.

RESULTS

Sixty-seven patients with shigellosis are included in this report. *Shigella flexneri* was cultured from the stools of 62 patients and *S. sonnei* from 5. The admission white blood cell counts from these patients ranged from 2,200 to 36,600 per cubic milliliter. Forty-five, or 67 per cent, of the patients had white blood counts of 11,000 per cubic milliliter or less. Seventeen, or 25 per cent, of the patients had white blood counts of 7,000 per cubic milliliter or less, and a number of these could definitely be described as representing

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Table I. Clinical data and leukocyte counts in patients with shigellosis

Patient No.	*Age*	*Duration of symptoms*	*Severity of illness*	*Leukocyte count*
1	3 years	18 hours	Severe	2,150
2	4 years	24 hours	Severe	2,200
3	2 years	24 hours	Severe	2,500
4	6 years	15 hours	Severe	3,800
5	9 years	8 hours	Moderate	4,950
6	4 years	12 hours	Severe	5,200
7	7 years	4 days	Severe	5,500
8	6 years	24 hours	Severe	5,600
9	2 years	5 days	Severe	5,800
10	2 years	18 hours	Moderate	6,000
11	9 months	4 days	Moderate	6,150
12	10 months	4 days	Moderate	6,500
13	3 years	24 hours	Severe	6,500
14	3 years	4 days	Severe	6,600
15	4 years	24 hours	Severe	6,650
16	2 years	24 hours	Moderate	6,650
17	2 years	6 days	Moderate	6,800
18	2 years	24 hours	Moderate	7,100
19	2 years	24 hours	Moderate	7,150
20	3 years	3 days	Moderate	7,200
21	17 months	24 hours	Severe	7,400
22	3 years	6 hours	Severe	7,400
23	4 years	24 hours	Severe	7,500
24	1 year	3 days	Moderate	7,700
25	2 years	2 days	Moderate	7,800
26	20 months	2 days	Moderate	7,800
27	10 years	16 hours	Moderate	8,000
28	2 years	10 hours	Severe	8,100
29	21 months	24 hours	Severe	8,100
30	14 months	24 hours	Severe	8,400
31	18 months	12 hours	Moderate	8,400
32	6 years	36 hours	Severe	8,650
33	19 months	36 hours	Severe	8,850
34	14 months	3 days	Moderate	8,900

a leukopenic response. Thus, the total leukocyte count in these patients varied from a rather marked leukopenia to a definite leukocytosis. This variation in leukocyte counts of the patients wtih shigellosis is shown in Fig. 1.

The differential blood counts in these patients tended to show the marked leukopenic response to be the result of a decrease in the polymorphonuclear neutrophils, whereas the elevated counts were due chiefly to an increase in this type of cell.

The ages of these patients ranged from 2 months to 9 years. No consistent correlation between age and either leukopenia or leukocytosis was noted. There was also no correlation between the severity of the illness and the leukocyte count; both moderately and severely ill children responded with a leukopenic, leukocytic, or normal white blood cell count. The white blood cell count of the only patient who died was 7,500. The response to therapy could be termed excellent in all patients except the one who died.

In general there was a greater tendency of the patients with a history of short duration of symptoms to have a normal or leukopenic response, whereas those with a longer duration of illness more often had a leukocytosis; however, there were exceptions in both groups of patients. Table I gives a summary of the association of age of the patient and the duration and severity of the illness with the white blood cell counts in these cases.

One of the constant reactions of experimental animals to the endotoxin of gram-negative organisms that has been described

Table I.—Continued

Patient No.	Age	Duration of symptoms	Severity of illness	Leukocyte count
35	2 years	20 hours	Moderate	8,900
36	19 months	24 hours	Moderate	9,000
37	2 years	4 hours	Severe	9,250
38	21 months	24 hours	Moderate	9,950
39	20 months	6 hours	Severe	9,600
40	15 months	12 hours	Severe	9,700
41	2 months	4 days	Severe	9,750
42	11 months	16 hours	Severe	10,050
43	5 months	3 days	Severe	10,150
44	4 years	24 hours	Severe	10,500
45	8 months	4 days	Moderate	10,600
46	16 months	24 hours	Moderate	11,150
47	4 years	4 days	Moderate	11,450
48	8 months	5 days	Moderate	11,750
49	23 months	3 days	Moderate	12,350
50	16 months	8 hours	Severe	12,500
51	9 months	5 days	Severe	12,600
52	1 year	24 hours	Severe	12,600
53	2 months	2 days	Severe	13,000
54	8 years	18 hours	Moderate	13,300
55	3 years	8 days	Moderate	14,400
56	17 months	12 hours	Moderate	14,450
57	2 years	24 hours	Severe	16,100
58	6 months	6 days	Moderate	16,900
59	18 months	24 hours	Severe	17,100
60	1 year	8 hours	Severe	19,100
61	4 months	2 days	Severe	19,250
62	6 months	15 days	Severe	19,450
63	4 months	2 days	Moderate	20,600
64	14 months	24 hours	Severe	27,500
65	4 years	4 days	Severe	28,250
66	18 months	24 hours	Moderate	31,200
67	20 months	6 hours	Severe	36,600

by Delaunay[3] in 1943, Bennett and Beeson[4] in 1950, and Thomas[5] in 1954 is the marked leukopenia which occurs after the intravenous injection of the endotoxin. This leukopenia develops very shortly after the administration of the endotoxin, persists for several hours, and is usually followed by a leukocytosis. This typical response in dogs to a single injection of crude endotoxin prepared from *S. flexneri* organisms is shown in Table II.

A possible explanation for the marked variation of leukocyte counts in patients with shigellosis may be found in the response of the individual to endotoxin elaborated by the organism in the gastrointestinal tract and absorbed by the patient. Smith, Platou, and Good[6] have suggested that the leukopenia found in some newborn infants with septicemia caused by gram-negative organisms is due to endotoxin from these organisms.

In the patient with an actual infection caused by the Shigella organism there is obviously not just a single time of absorption of the endotoxin comparable to that in the above experiments, but there is a continued absorption of the material. To simulate this situation more closely in an experimental animal, crude Shigella endotoxin was diluted in 500 ml. normal saline and administered intravenously in a constant drip of approximately 1.5 ml. per minute over a 5 to 6 hour period to dogs anesthetized with Nembutal, and blood counts were obtained at intervals during this period. The amount of crude endotoxin varied from 0.05 ml. to 1 ml. per kilogram of body weight. The leukocyte response in 10 dogs receiving a con-

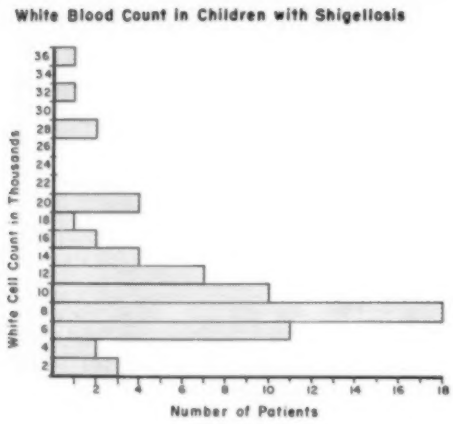

Fig. 1.

tinuous intravenous infusion of the diluted endotoxin is shown in Table III. It will be noted that all the animals developed a leukopenia within 30 to 60 minutes after the infusion was started. Some of the counts remained at leukopenic levels during the entire period of infusion, whereas others returned to preinfusion values or in some instances to values representing definite leukocytosis in spite of the continued administration of the endotoxin. Thus, even in this short period of observation, the leukocyte response in an experimental animal receiving a continuous infusion of endotoxin may be variable.

It does not seem too unreasonable to assume that a similar phenomenon could and does occur in the patient with shigellosis, and that leukocyte counts taken at various times during the illness might be normal, low, or elevated as we have observed in our patients.

COMMENT

The findings presented regarding the variation of white blood cell counts in patients with shigellosis are in accord with a number of other reports in the literature.[7-10] The fact that there can be such a variation in the white blood cell count of patients with bacillary dysentery makes the routine white blood cell count of very little use in the diagnosis of this condition. It seems worthwhile to reemphasize the fact that a low white blood cell count in a child with diarrhea does not make the diagnosis of a viral infection and exclude a bacterial etiology, thus altering the management of the patient with regard to antibiotics or chemotherapy. Obviously, other factors such as history, physical findings, etc., are taken into consideration in making a diagnosis and managing any patient.

The idea presented here as to the continued absorption of the endotoxin being capable of producing the picture of either a leukopenic or leukocytic response, depending on the time at which the count was obtained, is attractive to us. Felsen[7] has postulated that the leukopenic (agranulocytic) type of picture seen in some patients with shigellosis may be due to the destruction of the circulating leukocytes or to the necrotizing action of the endotoxin upon the vascular sinusoids of the bone marrow. Delaunay[3] has attributed the leukopenic response to endotoxin to the retention of the leukocytes in the capillaries of the lungs, liver, and spleen. The fate of these leukocytes is unknown; that is, whether they are eventually reintroduced into the circulation or actually destroyed.

Table II. Leukocyte response in dogs receiving a single intravenous injection of Shigella endotoxin

Time (hours)	*Dog 1*	*Dog 2*	*Dog 3*	*Dog 4*
0	10,600	7,000	16.500	14,500
1	3,000	2,100	2,500	3,500
2	3,000	2,100	6,500	3,000
3	2,200	8,500	22,000	6,500
4	4,000	10,800	29,000	14,000
5	11,500	14,000		

Table III. Leukocyte response in dogs receiving Shigella toxin by continuous intravenous infusion

Time (hours)	*Dose of toxin*									
	0.05 ml./Kg.		*0.1 ml./Kg.*		*0.2 ml./Kg.*		*0.5 ml./Kg.*	*1 ml./Kg.*		
	Dog 1	*Dog 2*	*Dog 3*	*Dog 4*	*Dog 5*	*Dog 6*	*Dog 7*	*Dog 8*	*Dog 9*	*Dog 10*
0	6,000	8,700	32,000	8,050	5,900	10,000	11,200	11,000	12,000	15,000
½	4,000	2,300	5,000	2,200	3,050	6,200	6,100	7,000	8,000	2,200
1	3,000	950	3,100	2,500	650	1,950	2,900	1,150	6,000	4,400
1½	1,400	1,900	3,000	3,050	900	6,900	7,000	1,350	5,700	2,100
2	3,100	2,150	1,300	4,000	750	5,000	2,700	2,350	2,100	13,000
2½	5,300	2,800	2,700	4,200	750	8,000	4,400	2,400	3,400	6,000
3	5,300	2,600	3,800	3,900	1,050	6,050	2,450	2,150	2,300	9,000
3½	5,500	2,600	4,000	4,750	1,400	14,000	3,400	2,100	3,300	10,000
4	5,400	8,000	6,050	2,800	800	12,000	3,450	2,350	2,600	16,000
4½	8,050	4,000	4,950	6,000	800	15,000	6,100	2,050	2,350	12,000
5	10,500	5,900	11,000	6,200	2,250	19,000	5,600	2,500	1,750	15,000
5½					1,100	23,000	5,750	2,850		
6					1,000	26,000				

SUMMARY

A review of the white blood counts of a group of patients with shigellosis reveals counts ranging from 2,200 to 36,600 per cubic milliliter. There were a number of patients with definite leukopenia, a number with leukocytosis, and a number with perfectly normal white blood cell counts. The idea that the continued absorption of the Shigella endotoxin is capable of producing this picture of variation in leukocyte response is presented. The marked variation in the white blood cell count in patients with shigellosis makes the simple procedure of a white blood cell count of little use in the differential diagnosis of bacillary dysentery.

REFERENCES

1. Donald, William D., Winkler, Charles H., Jr., and Bargeron, L. M., Jr.: The Occurrence of Convulsions in Children With Shigella Gastroenteritis, J. PEDIAT. **48:** 323, 1956.
2. Donald, William D., Winkler, Charles H., Jr., and Hare, Kendrick: Investigations on the Mechanism of the Leukopenic Response to Shigella Endotoxin, J. Clin. Invest. **37:** 1100, 1958.
3. Delaunay, A.: Mise en évidence d'une nouvelle propriété des antigènes glucido-lipidiques: Leur pouvoir leucopenisant, Comp. rend. soc. biol. **137:** 589, 1943.
4. Bennett, I. L., and Beeson, P.: Properties and Biologic Effects of Bacterial Pyrogens, Medicine **29:** 365, 1950.
5. Thomas, L.: The Physiological Disturbances Produced by Endotoxins, Ann. Rev. Physiol. **16:** 467, 1954.
6. Smith, Richard T., Platou, Erling S., and Good, Robert A.: Septicemia of the Newborn, Pediatrics **17:** 549, 1956.
7. Felsen, Joseph: Bacillary Dysentery, Colitis and Enteritis, Philadelphia, 1945, W. B. Saunders Company, p. 110.
8. Cooper, M. L.: Diarrhea and Vomiting in Children, Ohio M. J. **36:** 759, 1940.
9. Macumber, Harold H.: Acute Bacillary Dysentery, Arch. Int. Med. **69:** 624, 1942.
10. Roberts, Thomas L., and Daniels, Worth B.: Succinylsulfathiazole in the Treatment of Bacillary Dysentery, J. A. M. A. **122:** 651, 1943.

The electrocardiogram in infants of diabetic mothers

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THE purpose of this paper is to report the electrocardiographic findings in 21 newborn infants of diabetic mothers. Since both congestive failure[1, 2] with cardiomegaly[3] and potassium depletion secondary to hyperadrenocorticism[4, 5] have been suggested as factors contributing to the high neonatal mortality rate in infants born to diabetic mothers, the electrocardiogram would seem to be a potentially valuable tool for investigation of this problem. Zigler described upright T waves in V_1 and V_2 persisting after the first 24 hours of life, and in his book he gave an example of this in an infant of a diabetic mother[6] but concluded that "similar observations have not been made sufficiently frequently to be able to offer any detailed explanation of these findings." Bjorklund[5] described abnormalities of the T waves and S-T segment as well as "pathological U waves" in 10 of 15 newborn infants of diabetic mothers. Koss[7] described one infant with collapse and "electrographic evidence" of hypokalemia at 13 hours which responded to potassium chloride by stomach tube. In general, the literature reveals that experience with the electrocardiogram in the newborn of diabetic mothers is quite limited.

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MATERIALS AND METHODS

Forty-five electrocardiograms were taken on 21 newborn infants of diabetic mothers from 2 hours to 4 months after delivery. In ten instances the electrocardiograms were taken during the first 12 hours; 13 were taken within the first 24 hours; an additional 9 in the second 24 hours; 13 from 2 to 5 days; 4 during the second week of life; and 7 from 22 days to 8 months after birth. Seventeen infants had their initial ECG within the first 48 hours of life.

All electrocardiograms were taken with a Sanborn single channel, direct writing ECG machine at the standard paper speed. The 3 standard limb leads and 3 augmented unipolar limb leads were obtained in all cases and as many as possible of the following precordial leads were obtained: V_{6R}, V_{4R}, V_1, V_2, V_4, V_6, and V_9. Standard infant electrodes were used. No sedation was used prior to the taking of the tracings. Mean P, QRS, and T axes on the frontal plane were estimated by the method de-

scribed by Grant.[8] Tracings were also analyzed for rate, rhythm, P-R intervals in standard limb Lead II, maximum QRS duration, and maximum height of P and T waves in the limb leads and precordial leads.

The babies in this series were delivered during the estimated thirty-seventh week of gestation or upon the appearance of calcification of the distal epiphysis of the femur.[9] The medical, obstetric, and pediatric management of these cases has been described in a previous report.[10]

RESULTS

Average, minimal, and maximal values for rate, P-R intervals, QRS duration, Q-T index $\sqrt{Q\text{-}T}$, and mean QRS and T axes on the frontal planes are compared in Tables I through VI with values reported by Zigler[6] in normal infants. Findings falling outside the minimal or maximal values as reported by Zigler are noted by an asterisk. In most instances where the Q-T index exceeded .450 either a definite or probable U wave was present. These are reported as the "Q-U" index in Table VII. Although the number of tracings in this series is too small to be statistically comparable, the average values are quite close to those in Zigler's normal infants and, except for heart rate, in only one case (T axis of –20 at 8 days) did any of the measurable factors fall outside the range of normal as described by Zigler.

One of the 46 tracings was obtained at 5 hours on an infant who died at 24 hours and at autopsy showed complete transposition of the great vessels. The tracings in this case showed marked left axis deviation (mean QRS on the frontal plane of –45 degrees), an "adult" QRS pattern in the V lead (small R and deep S waves in the right V leads and high R and small S waves in the left V leads), high peaked P waves and diphasic P_{V_1} and P_{V_2} with late inversion (Fig. 1). This tracing was not included in the series for comparison with normal values as described by Zigler.

One tracing at 96 hours showed ventricular premature beats and one tracing at 4 days showed occasional complexes with "pre-excitation" (short P-R interval, increased duration of the QRS, and abnormal route of depolarization of the ventricles); otherwise, sinus rhythm was present in all tracings.

Beginning inversion of the T in V_1 and V_2, consisting first of inversion of the late portion of the S-T segment, was found in all cases after the first 24 hours, and inversion of the T waves was complete in these leads in all tracings taken one week or more after birth. In only one infant with tracing at 3 hours did the limb leads show any definite abnormality of the S-T segment or T wave (Fig. 2). This consisted of a depression of the S-T segment in the limb leads with the T forces for the most part buried in the depressed S-T segment. Actually there was no impressive "sagging" of the S-T segment.

A prominent finding was the frequent presence of prominent upright U waves in lead V_{4R} to V_4, usually largest in V_1 and V_2 during the first week of life (Fig. 3). Fourteen control electrocardiograms on infants of nondiabetic mothers showed similar prominence of the U waves during the first week of life (Fig. 4). In most leads the U wave was fused partly or completely with the T waves, but in one or more precordial leads one could find either complete separation of the T and U or "notching" at the site where the T-U junction would be expected from the Q-T interval in other leads. U waves were suspected in the limb leads of a few tracings in both infants of diabetic mothers and the normal controls, but their presence could never be definitely demonstrated to our satisfaction. Although Surawicz and associates[11] state that "determination of the shape and polarity of the U wave is impossible when the heart rate is above 96 min.," we felt that the definite presence and general polarity of the U wave could be deduced in some cases with rates up to 140 per minute by inspection and comparison of various leads. There was a tremendous variation in the heart rate of

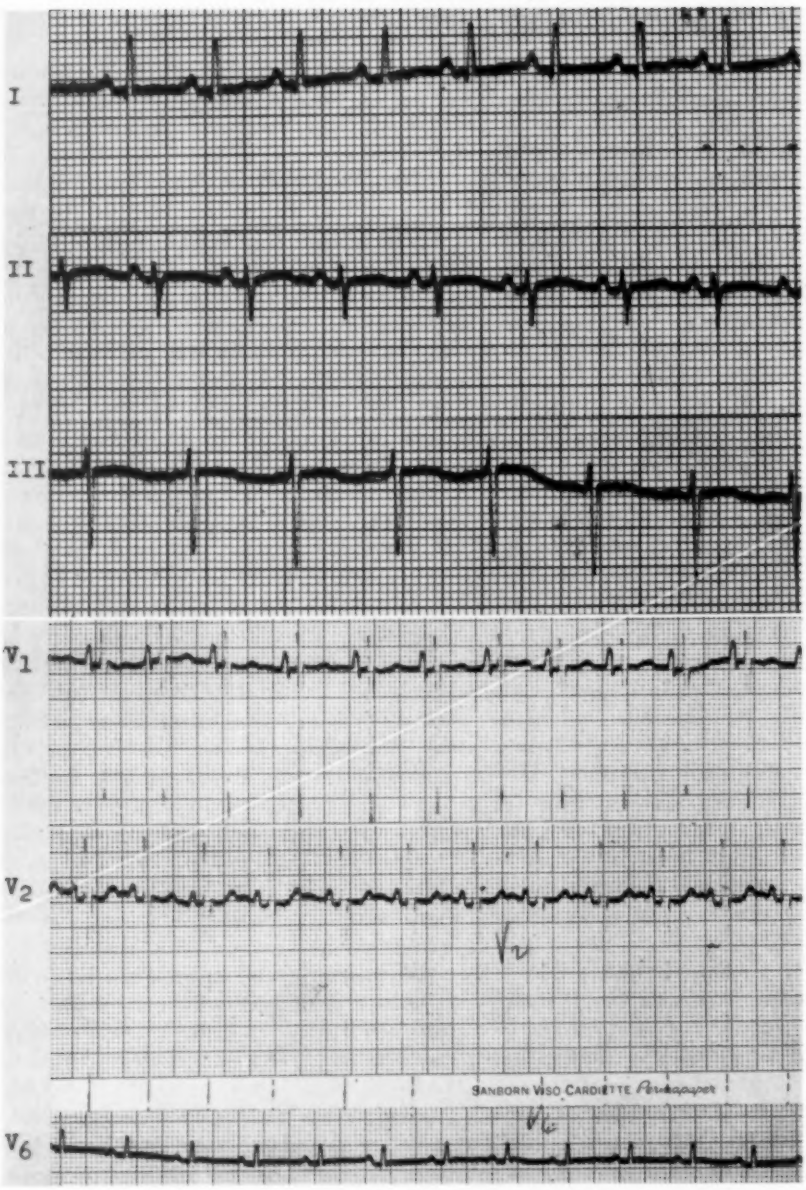

Fig. 1. Electrocardiogram taken 5 hours after delivery. Postmortem examination showed complete transposition of great vessels. Marked left axis deviation, prominent peaked P waves, diphasic P_{V_1} and P_{V_2} and "adult" type of QRS in V leads.

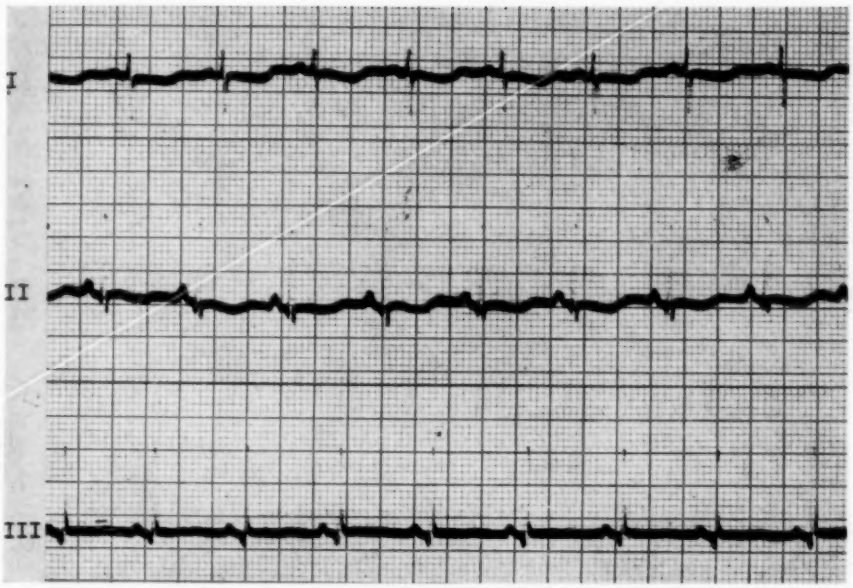

Fig. 2. Standard limb leads in newborn infant of diabetic mother at 3 hours, showing depressed S-T segments in Leads I and II with upright T or U (?) in Lead I.

many of these infants throughout the period the electrocardiogram was being taken, and rates considerably slower than the average could frequently be selected for inspection.

DISCUSSION

The hypothesis that most of the abnormalities of newborn infants of diabetic mothers (edema, excessive erythropoiesis, splanchnomegaly, etc.) are due to hyperactivity of the adrenal cortex[4] is an attractive one and has some suggestive support in the form of increased 17-hydroxycorticosterone in the amniotic fluid of diabetic mothers (a single case with 3 nondiabetic controls)[12] and increased urinary corticoid excretion in newborn of diabetic mothers.[13] Wolman[14] reported failure of an infant of a diabetic mother to show the usual drop in eosinophil count following the injection of 5 mg. of ACTH, but the eosinophil count was extremely low prior to ACTH injection, and this failure to respond could as well be interpreted as a result of maximum stimulation prior to ACTH injection. If such adrenal cortical hyperactivity were present, one might quite logically expect potassium depletion with characteristic electrocardiographic abnormalities. This has been suggested by Bjorklund on the basis of 4 serum potassium levels[5] and has been implied by Koss.[7] Studies based on electrolyte excretion[15, 16] have led to conflicting conclusions. Since other factors, including cardiodynamic adjustment to extra-uterine life, may affect the electrocardiogram, an ideal study should include serum potassium levels, electrolyte excretion, x-ray examination to determine heart size, and possibly cardiac catheterization studies. The precarious position of these infants during the first 48 to 72 hours of life, however, makes extensive study and manipulation of them extremely hazardous. Perhaps the greatest criticism of our own study rests on the fact that electrocardiograms were not taken in some instances during the first 48 hours because it was felt unsafe to remove these infants from the "air-lock" for this procedure. In the fu-

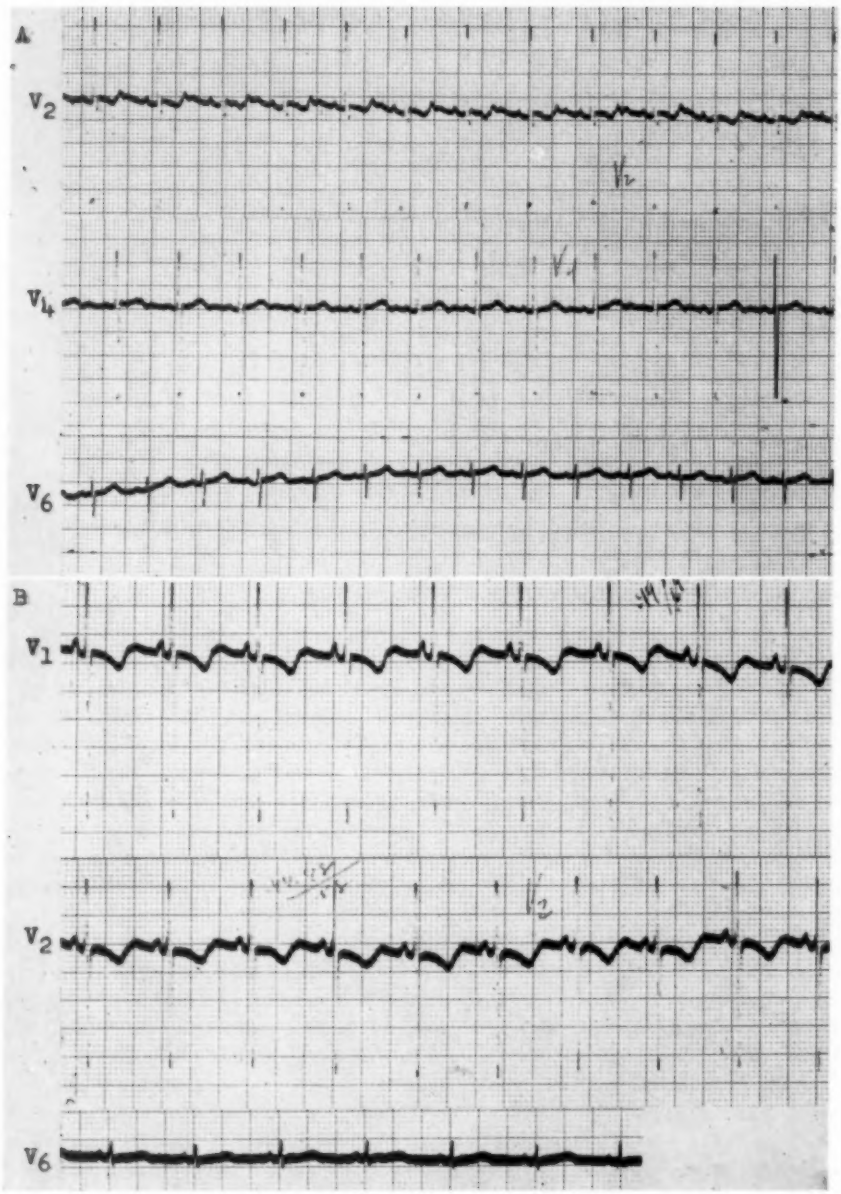

Fig. 3. *A*, Infant of diabetic mother 5 days after delivery, showing U waves in Leads V_2 and V_4 with partial fusion of T and U in V_2. *B*, Infant of diabetic mother 25 hours after delivery, showing upright T_{V_6} with Q-T interval of .30 and probable diphasic T fused with upright U in V_1 and V_2. Q-U interval of .44 to .46 in V_2.

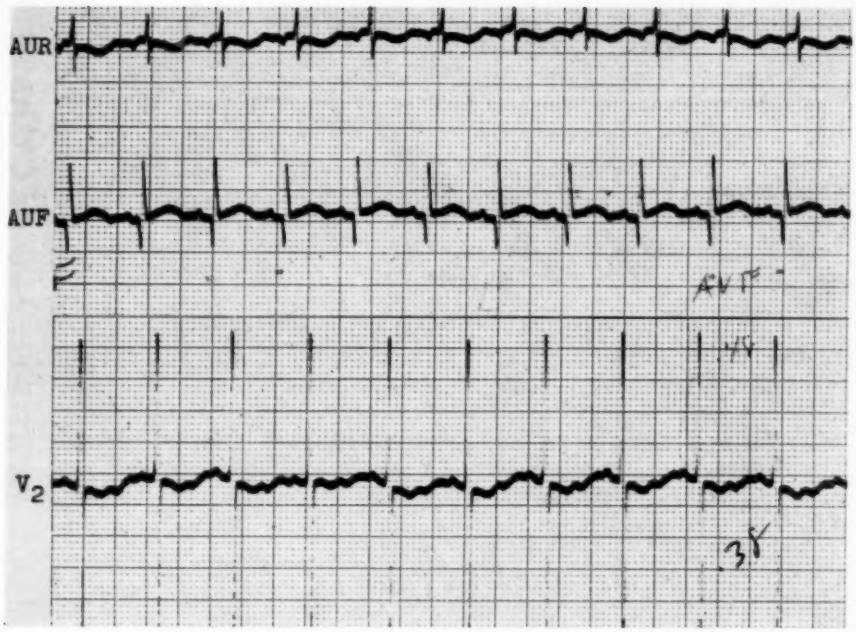

Fig. 4. Upright U wave in Lead V_2 and possibly in a V_R in normal infant of nondiabetic mother 24 hours after delivery.

ture we shall attempt to get at least the 3 standard limb leads on all infants during the first 24 hours of life. The few serum potassium levels we obtained on normal infants and infants of diabetic mothers showed such a wide range, probably because of varying degrees of hemolysis, that we felt no conclusions could be drawn. It would be of considerable practical importance to demonstrate the presence of hypokalemia in this group of infants since this would mitigate against the practice of glucose administration as well as suggest the administration of potassium. All babies in this series received subcutaneous injections of 60 to 75 c.c. of 2.5 per cent glucose every 8 to 12 hours during the first 24 to 48 hours, which might tend to aggravate any tendency toward hypokalemia.

There are two possible explanations for the low incidence of "abnormal" electrocardiograms in this series compared with the findings of Bjorklund. First, as mentioned above, electrocardiograms were not taken on a few of the sickest babies in this series during the first 48 hours. Second, the relative paucity of electrocardiographic studies in normal infants in this age group will undoubtedly result in differences of interpretation as to whether or not the tracing is within normal limits. Inverted T waves in the limb leads are cited by Bjorklund as one abnormality, and inverted T waves in Lead I were found in 2 of our infants during the first day of life. However, Zigler found the mean T axis as far to the right as ±180 degrees during the first day of life, which would allow inverted T waves in Leads I and II, and as far to the right as +110 degrees from one day to one week, which would allow inverted T waves in Lead I. Prolongation of the Q-T interval is another abnormality described by Bjorklund, but the wide range of normal values described by Zigler would make actual values for the Q-T interval or Q-T index desirable when this is reported as an abnormality. The U waves in Bjorklund's

Table I. Heart rate

	Zigler			*Present series*			*No. of cases*
	Average	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*	
First day	125	88	166	146	110	185*	13
1 day to 1 week	138	100	188	139	90	210*	25
1 week to 1 month	162	125	188	158	140	180	6

*See text.

Table II. P-R interval

	Zigler			*Present series*			*No. of cases*
	Average	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*	
First day	.099	.08	.12	.11	.09	.12	13
1 day to 1 week	.095	.08	.12	.093	.08	.12	25
1 week to 1 month	.095	.08	.122	.103	.09	.12	6

Table III. QRS interval

	Zigler			*Present series*			*No. of cases*
	Average	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*	
First day	.065	.04	.10	.045	.04	.06	11
1 day to 1 week	.056	.04	.08	.047	.04	.06	22
1 week to 1 month	.055	.04	.07	.052	.04	.06	6

Table IV. Q-T index ($\sqrt{Q\text{-}T}$)

	Zigler			*Present series*			*No. of cases*
	Average	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*	
First day	.421	.366	.533	.417	.353	.483	11
1 day to 1 week	.402	.322	.476	.402	.356	.449	20
1 week to 1 month	.386	.345	.434	.398	.375	.410	6

Table V. Mean QRS axis frontal

	Zigler			*Present series*			*No. of cases*
	Average	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*	
First day	137	75	190	115	75	180	13
1 to 7 days	128	75	190	119	75	160	22
1 to 4 weeks	105	-5	180	117	90	130	6

Table VI. Mean T axis frontal

	Zigler			*Present series*			*No. of cases*
	Average	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*	
First day	77	-10	180	58	-10	180	10
1 to 7 days	34	-30	110	14	-30	60	20
1 to 4 weeks	41	-10	130	15	-20*	45	6

*See text.

Table VII. Q-U index ($\sqrt{Q\text{-}U}$), present series

	Average	*Minimum*	*Maximum*	*No. of cases*
First day	.497	.473	.454	8
1 to 7 days	.479	.520	.585	15
1 week to 1 month	—	—	—	—

illustrations are questioned by the author himself in the descriptions appearing under the illustrations. At first we suspected that the prominent U waves and fused TU complexes occurring in the V leads in our tracings might be the result of electrolytic abnormalities, but the equal prominence of this finding in 14 control electrocardiograms of normal infants during this same period of life suggests that this is a normal finding for this age group, whatever the cause.

It is possible that the tendency for the mean T axis normally to lie somewhat further to the right, as well as the upright T_{V1} and T_{V2} during the first 24 hours and possibly the prominent U wave,[17] may represent a response of the left ventricle to the sudden increase in load imposed by adjustment to extra-uterine life. Hypervolemia may be inferred in infants of diabetic mothers from the presence of polycythemia and hydremia, which might increase the strain normally imposed on the left ventricle by circulatory changes occurring at and immediately following birth. This would be a logical explanation of the upright T_{V1} and T_{V2} persisting after the first 24 hours in babies of diabetic mothers, as described by Zigler, and could conceivably explain the S-T segment changes occurring in one of our tracings during the first day of life. In any event, we feel it is somewhat premature for a review article to state that "serial ECG's for potassium deficiency, electrolytes, pH and total eosinophil count may aid management during the first eight hours."[18] We do not feel that the extensive manipulation incident to such studies is warranted based on existing information, except for research purposes.

SUMMARY

Forty-six electrocardiograms taken on 21 newborn infants of diabetic mothers (30 tracings during the first week of life) fell within the limits of normal as described by Zigler except for S-T abnormalities occurring in one infant during the first day of life and one tracing with a main T axis of –20 degrees at 8 days. The ECG abnormalities occurring in a case of complete transposition of the great vessels are described separately.

The evidence that electrocardiographic abnormalities described by others in newborn infants of diabetic mothers may be due to potassium depletion is discussed, and the possibility is presented that these abnormalities may be due to an exaggeration of the increased load on the left ventricle secondary to circulatory changes occurring following delivery. From this small series we would conclude that abnormal electrocardiograms are uncommon in newborn infants of diabetic mothers and that the explanation of such abnormalities remains speculative.

We wish to express our appreciation to Dr. Bernie Brimhall for technical assistance in this study.

REFERENCES

1. Tolstoi, E., Given, W., and Douglas, C. G.: Management of the Pregnant Diabetic, J. A. M. A. **153:** 998-1002, 1953.
2. Lendrum, F. C.: The "Pulmonary Hyaline Membrane" as a Manifestation of Heart Failure in the Newborn Infant, J. Pediat. **47:** 149-156, 1955.
3. Miller, H. C., and Nielson, H. M.: Macrosomia, Cardiac Hypertrophy, Erythroblastosis and Hyperplasia of the Island of Langerhans in Infants Born to Diabetic Mothers, J. Pediat. **23:** 251-266, 1943.
4. Shelby, D.: The Critical Period in Infants Born of Diabetic Mothers, Bull. Moore-White M. Found. **5:** 24-47, 1954.
5. Bjorklund, S. I.: Children of Diabetic Mothers—Electrocardiographic Studies in the Newborn, Acta Paediat. **42:** 526-534, 1953.
6. Zigler, R. F.: Electrocardiographic Studies in Normal Infants and Children, Springfield, Ill., 1951, Charles C Thomas, Publisher.
7. Foreign letters: J. A. M. A. **156:** 222, 1954.

8. Grant, R. P.: Clinical Electrocardiography, New York, 1957, McGraw-Hill Book Company.
9. Whitely, J. M., Adams, T. W., and Parrott, M. H.: Diabetes and Pregnancy, West. J. Surg. **61:** 439-447, 1953.
10. Stephens, J. W., Holcomb, B., and Page, O. C.: Pregnancy and Diabetes. Results of Management Without Female Sex Hormones, J. A. M. A. **161:** 224-226, 1956.
11. Surawicz, B., Kemp, R., and Bellet, S.: Polarity and Amplitude of the U Wave of the Electrocardiogram in Relation to That of the T Wave, Circulation **15:** 90-97, 1957.
12. Hoet, J. P.: Adrenocortical Function in Infants of Diabetic Mothers, Symposia on Quantitative Biology **19:** 82-85, 1954.
13. Bjorklund, S. I.: Infants of Diabetic Mothers With Special Reference to Neonatal Adrenocortical Function as Assessed by Urinary Excretion of Corticoids and Tests Using Adrenocortical Hormone, Acta endocrinol. **15:** 25-32, 1954.
14. Wolman, B.: The Function of the Adrenal Cortex in the Newborn, Arch. Dis. Childhood **27:** 283-285, 1952.
15. Lowrey, G. H., Graham, B. D., and Tsao, M. V.: Clinical Homeostasis in Newborn Infants of Diabetic Mothers, Pediatrics **13:** 527-534, 1954.
16. Stapleton, T.: The Pattern of Electrolyte Excretion in the Urine of Babies Born to Diabetic Mothers, Arch. Dis. Childhood **31:** 42-43, 1956.
17. Lepeschkin, E.: Genesis of the U Wave, Circulation **15:** 77-81, 1957.
18. Editorial: Infants Born of Diabetic and Prediabetic Mothers, M. Times **85:** 951-955, 1957.

Drug allergy in pediatric practice

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THE problem of drug allergy, although an ever-increasing one in the practice of medicine,[21] has been relegated to a secondary role in the literature.[62] The paucity of reports of drug sensitivities in the current American pediatric literature indicates that this is particularly true in pediatrics. Since every drug is a potential allergenic agent[73] and from 1938 to 1959 there were over 11,000 new drugs licensed in the United States,[20] the scope of the problem for practicing physicians in this country who annually issue about 790,000,000 prescriptions is apparent.

This review of drug allergy will concern itself with terminology, factors influencing sensitization, manifestations, prevention and treatment, and a discussion of these mechanisms involved in allergic drug reactions.

DEFINITIONS

A *drug* is any substance used in the treatment or prophylaxis of disease. The Committee on Nomenclature of the New York Association of Allergy Clinics defines *allergy* as "any specifically acquired alteration in the capacity of living tissue to react. This alteration in capacity to react results from exposure to an exciting agent and is manifest upon reexposure to the same or to an immunologically related agent." The demonstration of specific antibody is not inherent in the definition. *Hypersensitivity* will be used interchangeably with *allergy*.

Drug idiosyncrasy is "an abnormal or unusual response to a drug"; it is manifested by a pharmacodynamic action which is either much greater than would be anticipated (intolerance) or of an unusual pattern.[43]

Among recent descriptions of the exact physiochemical nature of this type of drug reaction is the hemolytic anemia which occurs in about 10 per cent of American Negroes who receive an average dose of primaquine. With large enough dosage the hemolytic anemia would occur in all individuals. According to Motulsky,[81] in the group demonstrating this drug idiosyncrasy, there is a decrease in the number of nonprotein sulfhydryl groups in the red blood cells. This is related to the defective activity of glucose-6-phosphate dehydrogenase; the defect is transmitted by a sex-linked gene of intermediate dominance.

This abnormal metabolism of erythrocytes can be found in other ethnic groups and is involved in hemolytic anemias caused by an ever-growing list of agents. At present the list includes naphthalene, vitamin K, sulfisoxazole, nitrofurantoin (Furadantin), furazolidone (Furoxone), and fava beans.[5] Furthermore, it has recently been reported that a similar deficiency of reduced glutathione may exist in erythrocytes of normal

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newborn and premature infants.[113] This would mean that infants during this period are subject to hemolytic anemias of this type and that drugs in the above list may be dangerous particularly to premature infants.

Drug toxicity is an expected pharmacologic reaction that occurs in a large majority of treated patients with similar dosage and time relationships. Disease itself may enhance the toxicity of drugs. For example, the toxicity of morphine becomes greater in the presence of liver disease (failure to detoxify), myxedema (depression in metabolic rate), or severe respiratory insufficiency (increased susceptibility of previously injured central nervous system regulatory center).

Side effects are expected, but sometimes undesired, pharmacologic reactions that occur during administration of a drug, e.g., the tachycardia following epinephrine administration or occurrence of nasal blockage with Rauwolfia administration.

Secondary effects of a drug are due to pharmacologic reaction altering a physiologic balance. For example, the occurrence of staphylococcal enteritis secondary to antibiotic administration.

FACTORS THAT INFLUENCE SENSITIZATION

A. Drug factors. It is difficult to predict the sensitizing capacity of a drug before it has had widespread clinical trial because of the over-all relatively low incidence of drug reactions. Any drug is potentially allergenic[73] because the same chemical radicals responsible for the antigenic qualities of a drug are usually responsible for its pharmacologic action.[62] With our present knowledge it is impossible to predict which drugs are going to prove significantly allergenic except for the following generalizations: (1) non-human sera will sensitize 90 per cent of individuals receiving them in sufficient quantities[106]; (2) a drug with a high capacity to sensitize the skin of the guinea pig is probably not suitable for topical use in humans, but this factor does not carry over to its sensitizing capacity when administered by other routes[73]; and (3) substances with marked chemical reactivity are strong sensitizers.[62]

B. Host factors. Certain features peculiar to the patient are significant in determining drug hypersensitivity. Individuals with a family or personal history of allergy show a greater tendency to develop drug allergies than do non-atopic persons.[41, 103] This is particularly true of the *immediate* reactions. Chase[23] bred families of guinea pigs with markedly different susceptibilities to sensitization. The incidence of drug allergy is greater in women than in men[3, 21]; children are less sensitive to drugs than are adults. There is no satisfactory explanation for these differences. The debilitated patient has an increased likelihood of being sensitized and drug-sensitized individuals are much more likely to acquire new drug allergies than are those without previous sensitization.[67]

C. Methods of administration. The amount and the duration of drug dosage are important. Repeated intermittent administration is more hazardous than continuous therapy.[67] The route of administration often affects the sensitizing index of the drug. The oral method is least likely to cause sensitization, the parenteral method is next most likely, and application to skin or mucous membrane produces sensitization most frequently. The status of the site of drug administration is also important; previously injured skin or other tissue is particularly susceptible.[43] A drug may have its allergenic qualities enhanced by administration in an absorption-delaying menstruum or with an adjuvant[67] (e.g., penicillin in oil causes a higher incidence of sensitivity than aqueous penicillin).

MANIFESTATIONS AND DIAGNOSIS

A drug must be suspected of producing any type of clinical manifestation whenever the latter is not easily explained by the patient's illness. The disturbance may be immediate or delayed. If the child has never received the drug, usually 7 to 10 days will elapse before an allergic reaction is noted; this is the time required for antibodies to

form. The diagnosis can be considered only by having this concept in mind. The diagnosis is then supported, if discontinuation of the drug leads to cessation of symptoms. Readministration of the drug is usually dangerous, although refractoriness often develops and results in false negative reactions. Occasionally a reaction may be due to the menstruum in which the drug is given. Skin tests are not very reliable, but if positive are significant. Eosinophilia is a good clue to the diagnosis. Certain symptoms such as fever, rash, and toxicity (headache, malaise) are commonly noted. At times it is very difficult to distinguish between a toxic and an allergic reaction. Cross reactions are frequent with such drugs as the sulfonamides, barbiturates, and phenothiazine derivatives.

A. Immediate reaction. The immediate types of reactions are: (1) anaphylaxis, (2) asthma, (3) rhinitis, (4) urticaria, angioedema, (5) eczema, (6) conjunctivitis, (7) gastrointestinal disturbances, (8) eosinophilic pneumonitis or Loeffler's syndrome. In order for a reaction to be classified as an immediate one, it must take place within 24 hours of the *eliciting* dose of the drug. The most severe reaction is the anaphylactoid one characterized by itching, hives, cough, dyspnea with "tight painful chest," pallor, sweating, tachycardia, vascular collapse, and death. Death has occurred in approximately 30 per cent of the cases.[106] Asthma and rhinitis usually occur in individuals who have previously had these symptoms.

B. Serum sickness (delayed) reactions. The delayed types of reactions occur from 48 hours to 4 weeks after drug administration but most commonly are seen between the seventh and tenth days. Serum sickness is the prototype. It is often due to the larger, more complex molecules of proteins and antibiotics but it may also be caused by sulfonamides and other simple compounds. The syndrome is characterized by fever, urticaria, angioedema, arthralgia, lymphadenopathy, and leukocytosis. Less frequently, peripheral neuritis, renal manifestations, and other symptoms are evident. Appearing between the seventh and tenth days of therapy, fever is one of the most frequent manifestations of drug allergy and is often accompanied by a rash. It may, however, be a very confusing symptom when it occurs following the administration of an antibacterial agent for a febrile illness. Drug fever is usually not serious, and occasionally the drug does not have to be discontinued.

C. Vascular reactions. Vascular manifestations such as polyarteritis nodosa and lupus erythematosus are more unusual forms of drug allergy, but are so serious that early diagnosis is imperative. Rich[89] first noted in 1940 that periarteritis nodosa could result from sulfonamide administration. Since then several other drugs have been involved.[43] McCombs[75] has suggested that these disease processes be classified as "allergic" vasculitis.

There are two types of vascular reactions. The first has a relatively long clinical course with gastrointestinal symptoms, hypertension, peripheral neuropathy, and secondary renal disease. The second form is a fulminating disease, characterized at first by fever, skin eruption, and other symptoms of serum sickness, and then rapidly progressing to nephritis, myocarditis, and often death. In the latter form there is most frequently a history of sulfonamide ingestion. There are certain differences between idiopathic forms of the disease and that produced by drugs. In many cases of "allergic" vasculitis of the lupus type, no LE cells can be demonstrated. The prognosis is fairly good when the disease is caused by a drug reaction because withdrawal will usually bring permanent remission. The ratio of males to females is more nearly equal in Apresoline-induced lupus than in the idiopathic form where the ratio is approximately 2.5:1.

D. Dermatologic reactions. By far the largest group of reactions in drug allergies are the dermatologic responses. Grant-Peterkin[45] states, "Drugs can provoke so many different types of dermatoses that in every patient with a cutaneous eruption, the possibility of a drug rash must be borne in mind." The most common one is contact

Table I. Drug eruptions produced by various agents*

Agent	*Urticarial*	*Purpuric*	*Morbilliform*	*Scarlatiniform*	*Vesicular*	*Pustular*	*Bullous*	*Seborrheic dermatitis*	*Contact-type eczema*	*Eczematoid*
Barbiturates	+	+ +	+ + +	+	+	+	+	−	−	+
Hydantoins	−	+	+ + +	+	−	−	+	−	−	−
Penicillin	+ + +	+	+	+	−	−	+	+ +	+ +	−
Streptomycin	+ + +	+	+	+	+	−	+	+ + +	+	+
Other antibiotics	+	−	−	−	−	−	−	+ +	+	+
Sulfonamides	+	+	+ +	+	+	+	+	+ +	+ +	+
Heavy metals	+	+	+	+	+	−	+	+	−	+
Halogens	+	+ + +	+	+	+ +	+ +	+ +	−	−	−
Salicylates	+ + +	+ +	+ +	+	+	−	−	−	+	+
Quinines	+	+	−	+ + +	−	−	+	+	+	+
Mepacrine	−	+	+	+	−	−	−	+	−	+
Phenolphthalein	+	+	−	−	−	−	−	−	−	+

*From Grant-Peterkin.[45]

dermatitis. It is also the form of drug allergy for which testing is most reliable. Such testing is performed by applying a patch containing the suspected offending agent to the skin and watching for a delayed reaction. Diagnostic patch testing reproduces the clinical conditions in miniature and there is good clinical correlation with the test results. The allergic reaction in contact dermatitis is due to the absorption of a drug which leads to formation of a conjugate that spreads throughout the skin via the lymphatics. Clinically the area of sensitivity tends to spread in a centrifugal direction from the primary area. Frequently noted in exacerbation of a dermatitis is an area of more marked "flare-up" at the original site of sensitization or at the site of previous patch testing. This phenomenon is probably related to increased antibody concentration at these sites.

Of the remaining forms of dermatitis due to drugs (Table I), special mention should be made of exfoliative dermatitis, which may constitute a severe and not infrequently fatal illness. The primary process in the skin is often accompanied by chills, fever, and enlargement of the liver and spleen. The massive loss of skin integrity leaves the patient vulnerable to infection as is the case with severe burns.

E. Hematologic reactions. Hematologic reactions are frequently serious. In allergic purpura the reaction is thought to involve not only the platelets but also the capillary endothelium.[2] Agranulocytosis and leukopenia may also result from the administration of therapeutic agents. Leukopenia due to leukocytic agglutins in "compatible blood" transfusions has been reported.[85] Aplastic anemia from drug therapy (sulfonamides, hydantoins, chloramphenicol, arsenicals and others) is probably a toxic reaction rather than an allergic one.[95, 100] Hemolytic jaundice is an extremely rare form of drug allergy.

F. Hepatic reactions. Allergic hepatitis has been caused by chlorpromazine, hydantoins, arsenicals, methyl testosterone, thiouracil, cincophen, para-aminosalicylic acid, diethylstilbestrol, phenobarbital, sulfadiazine, and prochlorperazine.[53, 78, 90] Jaundice appears about the seventh to the tenth day after drug administration. Inflammation of the intrahepatic bile ducts leads to jaundice, but such liver function tests as thymol turbidity and cephalin cholesterol flocculation are normal. There is infiltration of eosinophils in the periportal spaces and blood eosinophilia. Prompt recurrence of jaundice

Exfoliative dermatitis	*Photosensitivity*	*Dermatophytid*	*Pityriasis rubra pilaris*	*Erythema multiforme*	*Stevens-Johnson syndrome*	*Erythema nodosum*	*Lupus erythematosus*	*Periarteritis nodosa*	*Nodular vasculitis*	*Ulcerative or granulomatous*	*Lichenoid*	*Psoriasiform*	*Fixed drug eruption*	*Mucosal lesions*
+	++	–	–	++	++	–	+	–	–	–	–	–	++	++
+	–	–	–	–	–	–	–	++	–	–	–	–	–	+
+	+	++	+	+	+	+	–	+	+	–	–	–	+	+
+	++	+	–	–	–	–	–	+	+	–	–	–	–	++
–	+	+	–	+	–	–	–	+	+	–	–	–	+	+
+	+++	–	–	+	+	+	+	+	+	–	–	+	+	+
+	+	+	+	–	–	–	–	+	–	–	++	–	+	+
+	–	–	–	+	–	+	–	–	–	+++	–	–	+	+
–	–	–	–	–	–	–	–	+	++	–	–	–	+	+
+	–	–	–	–	–	–	–	–	–	–	–	–	+	+
++	+	+	++	–	–	–	–	–	–	–	+++	+	++	++
–	–	–	–	+	–	–	–	–	–	–	–	–	+++	+

takes place if the drug is readministered.[51] In chlorpromazine jaundice, critical examination of all possible mechanisms again leads to the conclusion that hypersensitivity is the most likely cause.[26]

G. Neurological reactions. Neurological reactions of drug allergies may involve almost any part of the nervous system. Radiculitis, polyneuritis, polyradiculoneuritis (Guillain-Barré syndrome), myelitis, Landry's ascending paralysis, and various meningeal and cerebral forms have been described.[41]

COMMON DRUGS AND THEIR REACTIONS

A. Sera and vaccines. The drugs most commonly used in pediatric practice are those concerned with the prevention and treatment of infectious diseases. The sera and vaccines primarily produce serum sickness and neurological manifestations. Occasionally they cause anaphylactic shock. Table II lists various sera and vaccines with their animal origin and available substitutes for them.

DPT rarely causes allergic reactions, although serious and even fatal reactions have been reported.[41] Silk antigen, present in vaccine due to filtration through silk screen, is responsible for some of the reactions that accompany this drug.[91] While the presence of allergic eczema in the patient or in any member of the household is a strong contraindication to smallpox vaccination, there is no such contraindication to routine immunization with DPT. Reactions in allergic children are no more frequent than in normal children.[48]

B. Antibacterial agents. At present penicillin is the most important antibacterial agent involved in drug allergy. More than 300 tons are produced annually in the U.S.[3] Feinberg[31] estimated in 1956 that there had been over 1,000 deaths in the United States due to anaphylaxis from penicillin. Deaths have been reported in children.[92] So potent an allergen is penicillin that as little as 0.000003 unit of penicillin has caused a systemic reaction.[10] Anaphylaxis has been reported with oral[9, 69] as well as with parenteral administration. All forms of penicillin are capable of causing sensitization. A marked increase in *reported* reactions has occurred since the introduction of procaine penicillin suspension.[3]

Almost every type of allergic drug reaction has been attributed to penicillin. Immediate and delayed reactions are about equal in incidence, if inconsequential skin eruptions are omitted. Other reactions include

Table II. Sera and vaccines capable of causing allergic reactions and available substitutes

Disease	*Source of antigen*	*Available substitute*	*Source of substitute material*
Tetanus	Horse serum	Bovine serum	Merck Sharp & Dohme
Gas gangrene	Horse serum	None	
Diphtheria	Horse serum	None	
Snake and black widow spider bites	Horse serum	None	
Pertussis	Rabbit serum	Human hyperimmune serum	Cutter Laboratories Hyland Laboratories Philadelphia Serum Exchange
Rabies	Rabbit brain tissue	Duck egg vaccine Horse serum	Eli Lilly & Company Lederle Laboratories
Poliomyelitis	Monkey kidney Horse serum (trace 1:5,000,000) Penicillin	"Penicillin-free" (0.003 u./ml.)	Wyeth Laboratories, Inc.
Influenza	Chick embryo	None	
Mumps	Chick embryo	Human hyperimmune serum	Hyland Laboratories
Equine encephalomyelitis	Chick embryo	None	
Yellow fever	Chick embryo	None	
Rickettsial diseases	Chick embryo	None	
DPT	Silk	Nylon strained	Lederle Laboratories

most forms of dermatologic responses,[45] Arthus type phenomenon,[94] polyarteritis nodosa,[77] drug fever, asthma, hepatitis, peripheral neuritis, hemolytic anemia, and granulocytopenia.[3]

Penicillin sensitivity may take place in less obvious ways: (1) in utero[41]; (2) from ingestion of milk (11.6 per cent of samples tested in one survey contained detectable quantities of penicillin[76]); (3) from atmospheric penicillin "fall-out" in hospitals and doctors' offices[44]; (4) from questionable cross-sensitivity between penicillium molds and penicillin[70]; and (5) from penicillin in poliomyelitis vaccine.[112]

Streptomycin and dihydrostreptomycin are used today so frequently in pediatrics with isoniazid and para-aminosalicylic acid that the discussion will include all of these drugs. Isoniazid very infrequently causes reactions and from this standpoint is almost an "ideal" drug according to Chapman.[22] Streptomycin produces skin disturbances primarily. The most common type is contact dermatitis seen in patients and nurses.[101] Reactions have resulted from the drug being transmitted through washed syringes that previously contained streptomycin. Fever is the most common systemic reaction; this occurred in 6.1 per cent of 3,000 patients.[55] Serum sickness may be observed. The rashes of streptomycin and of PASA are frequently so mild that they often disappear while therapy continues.[57] Exfoliative dermatitis necessitates cessation of the drug. Severe hematologic reactions are occasionally noted. Transitory eosino-

philia while not uncommon during prolonged streptomycin therapy is not serious enough to cause discontinuation of therapy. Streptomycin is unique in causing eosinophilia. Anaphylaxis is a rare complication.

The increased use of antituberculosis therapy on an outpatient basis in pediatrics demands an increased awareness of possible reactions to PASA. The physician should inform the parents about possible allergic reactions.

Of the remaining antibiotics, novabiocin is a significant sensitizer, causing allergic skin reactions in about 12.5 per cent of patients treated for 10 days or more; fatal reactions may occur.[16] Chloramphenicol has caused few allergic reactions; aplastic anemia and the "gray syndrome" in premature infants are considered to be toxic rather than allergic reactions.[21, 84, 95, 108]

Tetracyclines, bacitracin, neomycin, tyrothricin and vancomycin produce few allergic reactions[3] with occasional exceptions such as, for example, severe dermatitis due to tetracycline.[114] Tetracyclines administered parenterally are potentially as sensitizing as penicillin. There is too little experience to evaluate kanamycin and ristocetin. There are indications that ristocetin has a high index of sensitization.[38]

The sulfonamides will be considered as a group even though there are differences in their individual capacities to produce sensitization.[111] These compounds may excite almost any type of drug allergy.[3] Skin reactions and drug fever are common. Allergic vasculitis manifested by such disorders as renal disease, carditis, and hepatitis is the most dangerous lesion. While cross-reactions between different sulfonamides are frequent, the use of combinations of sulfonamide drugs is claimed to decrease the number of allergic and toxic reactions.[64]

C. Analgesics, sedatives, and anticonvulsants. These drugs are extremely important in pediatric drug allergy because they are used so frequently and indiscriminately. The principal reactions are dermatologic. Anaphylactic shock and asthma due to aspirin have occurred, as a rule, in known asthmatic individuals. The barbiturates can cross-react and often produce fixed drug reactions. The hydantoins (Dilantin, Mesantoin, Paradione and Tridione) can cause fatal reactions such as blood dyscrasia, exfoliative dermatitis, severe hepatitis, and periarteritis nodosa.

The phenothiazine derivatives used as tranquilizers produce many allergic reactions. Chlorpromazine has replaced streptomycin as a leading cause of contact dermatitis in nurses.[66] Fumes from open vials may cause reactions. Intrahepatic obstructive jaundice caused by chlorpromazine and prochlorperazine is considered an allergic reaction.[78] In chlorpromazine-induced jaundice, cross-reactions may occur with many other phenothiazine derivatives, for example, gentian violet, Phenergan, Pyrrolazote, Sparine, Compazine, Parsidol, and Depancol.[52] A great number of severe and bizarre neurological disorders which are not allergic reactions are caused by this group of drugs.[113]

Meprobamate has caused allergic reactions in about 1 per cent of incidences[6]; 73 per cent were dermatologic and 16 per cent serum sickness reactions. The oral ingestion of 250 mg. of the related compounds, mephenesin and Tolserol, has produced anaphylaxis and positive passive transfer skin tests have been demonstrated.[47]

D. Hormones and other protein drugs. Drugs of protein composition cause allergic reactions. The sensitization may be due to the drug itself or to the animal proteins from which it is derived. Dermatitis, urticaria, anaphylactic shock, serum sickness, and aplastic anemia have been caused by ACTH.[3] In reactions due to ACTH gel the bovine gelatin may be the sensitizing agent. By 1956, the third case of fatal anaphylaxis due to corticotrophin Z had been reported.[31]

Allergic reactions to insulin are rare in children except for local urticaria which disappears in a few weeks.[109] Antibodies, other than the skin-sensitizing antibodies, are invariably formed when insulin is given for 4 months or longer. Apparently these antibodies in usual concentration result only in insulin binding, but in high concentration result in insulin resistance.[40]

Table III. Sensitizing capacity of common dermatologic preparations*

Group	*No. of patients by percentage showing allergic reactions*	*Drugs included*
I	0%	Benzoic acid, benzyl benzoate ichthammol
II	0 to 2%	Boric acid, aluminum acetate, menthol, naphthalene, petrolatum phenol
III	2 to 5%	Oxycholesterol, petrolatum ointment, hydrous wool fat, dibucaine, resorcinol, salicylic acid, iodochlorhydroxyquin
IV	5% or more	Ammoniated mercury, ethyl aminobenzoate, red mercuric sulfide, crude coal tar, coal tar solution, juniper tar, tetracaine, ointment containing cetyl alcohol–coal tar distillate, near-colloidal sulfur, and salicylic acid; chlorhydroxyquinoline compound ointment, and benzoic and salicylic acid ointment N. F.

*According to Baer and associates.[7]

Other drugs containing protein involved in allergic reactions include posterior pituitary hormone, epinephrine, estrogens, androgens, trypsin, heparin, protamide, and pancreatin.[69] Recently buccal varidase has been reported to have caused immediate allergic reaction,[30] although it is possible that the tablet base may be the responsible substance.[37]

E. Antihistamines. The antihistamines may also be the source of allergic reactions.[33] They are such potent topical sensitizers that dermatologic preparations were removed from the 1953 edition of *New and Nonofficial Remedies*. In addition to a variety of dermatoses, the antihistamines have been associated with agranulocytosis and even anaphylactic shock.[33]

F. Miscellaneous drugs. Other drugs used in pediatric practice which have caused allergic reactions include: phenolphthalein, bismuth, arsenicals, iodides, bromides, mercurials, vitamins, thiouracils, codeine, radiographic contrast media, and dextran.

Baer and his co-workers[7] tested by patch application 743 patients who had shown skin intolerance to one or more dermatologic preparations. The medications tested were the ones commonly found on "dermatologic trays." Their results are shown in Table III.

PREVENTION AND TREATMENT

A history of allergy in the family or the child should alert one to the possibility that drug allergy may be more likely to occur. Previous drug allergy of any kind and particularly sensitivity to the drug in question are extremely important. *Believe the patient if he says he is allergic to a drug.*

Potentially dangerous drugs such as amidopyrine or chloramphenicol should be avoided whenever possible. The latter might be reserved for diseases for which there is no alternative antibiotic. If the drug is known to affect the hematopoietic system, the patient must be observed for such symptoms as sore throat, malaise, chills, and fever. Frequent blood counts may give advance warning of agranulocytosis.

Testing by the scratch, intradermal, or conjunctival methods is recommended before the administration of heterologous sera, radiographic media, and penicillin whenever there is a history suggestive of drug allergy. Skin tests to detect penicillin reactors is a controversial method.[24, 70] Smith[102] proposed that all individuals who are to receive parenteral penicillin should first have scratch and conjunctival tests with the same penicillin that is to be injected. He advises that the loaded syringe should be laid aside for 20 minutes, and that the injection should be given only if no reaction occurs. In his series there was one systemic reaction to the test itself; one young man who had a negative scratch test but a slightly positive conjunctival test received procaine penicillin from another physician one week later and died

within 15 minutes. The shortcomings of skin testing are: (1) failure to detect the patients who develop delayed reactions (serum sickness), (2) false positive and negative reactions, and (3) serious reactions to testing.

The development of penicillinase for clinical use has probably added a significant therapeutic tool for the management of penicillin allergy. Penicillinase is an enzyme produced by such bacteria as *Staphylococcus aureus, Escherichia coli,* and *Bacillus cereus.* It acts on penicillin by hydrolizing it to penicilloic acid which is not antigenic. Unfortunately, it is not bactericidal either. It is recommended in the treatment of delayed hypersensitivity reactions to penicillin and succeeds where steroids and hormones have failed.[79, 112] The reported action is so rapid, however, reducing serum penicillin levels to zero within 1 hour after intramuscular injection,[36] that it would seem logical to use it in penicillin anaphylaxis *after* certain emergency measures have been taken (see below). It may also be useful in establishing an etiological diagnosis, bearing in mind that frequent spontaneous remissions occur in penicillin allergy. Available as Neutrapen,* the usual dose of penicillinase is 800,000 units, given intramuscularly. Intravenous administration is contraindicated because severe reactions have been reported and sensitization has occurred.[53] It is frequently very painful and caution should be excerised in using it.[36]

Antihistamines have been given in conjunction with penicillin and radiographic media. It appears that antihistamines decrease the number of minor allergic manifestations without preventing anaphylactic or severe delayed responses.[39, 54, 72] This is a serious criticism because the milder reactions are often helpful in that they portend more serious reactions.

If sensitivity to local anesthetics is present, intradermal testing may be done. One should never test with a drug that has previously caused a reaction. Since cross-reactions occur among many of the local anesthetics, a very dilute solution, e.g., 1:1,000,000, is first used. If the test is negative, more concentrated solutions are made up progressively until a test dose in therapeutic strength produces no untoward response.

Reactions to DPT may be obviated in several ways. A preparation that is filtered through nylon may be used. The booster dose necessary to provide adequate immunologic response can be obtained with 0.2 ml.[48] In children over 6 years of age, the pertussis antigen may be omitted. A Schick test can determine if diphtheria toxoid need be given. Fluid toxoid using single immunologic agents can be given intradermally in a dose of 0.1 ml. The latter method provides good immunity and rarely causes adverse reactions.

If a drug must be given where there is a suspicious history, it should be given orally in small doses. Topical application, especially to injured skin or mucous membrane, is the method most likely to cause an allergic reaction. Prolonged intermittent administration tends to provoke more sensitivity than short effective courses. If the drug must be administered by injection it should be given in the arm or thigh rather than the hip, so that a proximal tourniquet may be used if an immediate reaction occurs. The patient will often warn of an impending severe immediate reaction by stating, "I feel funny." This patient complains of itching and tingling. Then one may observe hives, coughing, choking, dyspnea, wheezing, sweating, rapid thready pulse, and vascular collapse.

When such a reaction occurs, 0.5 ml. aqueous epinephrine 1:1,000 is immediately given intramuscularly in the opposite arm and repeated as often as necessary. The patient must be watched very closely for reaction to excessive amounts of epinephrine. If symptoms of overdosage appear, a tourniquet may be used to control the rate of absorption. At times the peripheral vascular collapse is so profound that there is no absorption of the epinephrine. In such instances artificial respiration combined with aerosol epinephrine may be lifesaving.[96] Epinephrine by the intracardiac route may also be used.

*Schenley Laboratories.

Table IV. Schedule of treatment with sera when skin test is positive*

Amount	*Dilution*	*Route of administration*	*Time of next dose*
0.05 c.c.	1:20	Subcutaneously	15 minutes
0.1 c.c.	1:10	Subcutaneously	15 minutes
0.3 c.c.	1:10	Subcutaneously	15 minutes
0.1 c.c.	Full strength	Subcutaneously	15 minutes
0.2 c.c.	Full strength	Subcutaneously	15 minutes
0.5 c.c.	Full strength	Intramuscularly	15 minutes
Full dose	Full strength	Intramuscularly	15 minutes

*Each subsequent dose is given only if there are no reactions. If an allergic reaction of any type occurs after an injection, one should drop back in the schedule to the last nonreacting dose and attempt to continue. It is probably safest to have an intravenous infusion going before beginning the procedure.

Above the site of the injected drug a tourniquet is placed and 0.2 ml. of epinephrine is infiltrated around the area. Intravenous antihistamine (10 mg. of Chlortrimeton or 20 mg. of Benadryl) is given, but is distinctly secondary in importance to the epinephrine. Oxygen is used for dyspnea and cyanosis. A tracheotomy is rarely needed to relieve obstruction from epiglottic or laryngeal edema. For profound circulatory failure an intravenous infusion (by cut-down if necessary) of levarterenol bitartrate is given. Later blood and/or plasma may be used to combat shock. ACTH or corticosteroids given intravenously have no place in the immediate treatment but are used as a supportive measure. Attempt to hasten the elimination or neutralization of the drug by use of specific substances such as penicillinase or BAL may be considered. A tray with all the necessary materials to carry out the emergency steps should always be readily available to anyone administering drugs.

For drug allergies of the delayed type there are two essential points in therapy: removal of the offending drug and symptomatic treatment. The single most important thing is to find the responsible drug; this is usually done by careful history taking. The parent should be questioned specifically about such common household remedies as aspirin, vitamins, nose drops, laxatives, cough mixtures, tonics, and the like. Penicillinase, BAL, and other drugs to neutralize the offending agent may be indicated. The symptomatic treatment consists primarily in the relief of itching, pain, fever, and various skin manifestations. A skin once sensitized becomes more susceptible to allergic reactions. An attempt should be made in the therapy of dermatologic manifestations to use substances that have a low index of sensitivity. ACTH and corticosteroids are used if the allergic reaction produces severe discomfort, interference with necessary therapeutic procedures, or a threat to the patient's life.[67] Blue[14] has reported good results in urticaria and serum sickness with histamine iontophoresis.

There are several procedures for desensitization to a drug when an existing or a latent allergy is present. If the skin or conjunctival test is positive and serum such as tetanus antitoxin must be administered, the schedule in Table IV is recommended.

When severe allergic reactions to insulin occur, the latter may be continued by using one of three methods.[83] If the animal protein rather than the insulin causes the sensitivity, insulin from a different animal is used; unmodified insulin may be made much less allergenic by boiling the vial in water for 15 minutes. This reduces the antiglycemic potency to about one half. After 2 to 4 weeks of such treatment, desensitization is accomplished and then other forms of insulin may be used safely. Finally, rapid "desensitization" may be employed in which the amount of insulin is reduced and then rapidly increased to previous levels with the antireactive protection of ACTH or a corticosteroid.[56]

For desensitization to other medications

which must be continued in spite of delayed allergic reactions, the recommended procedure is to reduce the dose and then gradually build it up again. For example, in tuberculosis 50 mg. per day of para-aminosalicylic acid is given and increased gradually to the full amount over a 14 to 28 day period. Since spontaneous disappearance of symptoms may take place when the allergenic drug is continued in full dosage, it is speculative whether this procedure actually constitutes active desensitization.[21] At times it is possible to use a more rapid desensitization schedule or to continue the drug in full amounts under the "cover" of concurrently administered ACTH or corticosteroid drugs.[56]

MECHANISMS INVOLVED IN DRUG ALLERGIC REACTIONS

"It is believed that drugs that cause hypersensitivity act as haptens. Once the patient becomes sensitized, a minute dose of the drug will evoke some type of allergic response."[43] Haptens are substances of relatively low molecular weight which alone are not antigenic but when combined with proteins form antigenic conjugates. The concept of hapten formation provides the most acceptable explanation of drug allergy. The classical studies of Landsteiner[59] and others have been reviewed. Their pertinent findings will now be discussed.

The combination of a hapten with homologous serum protein or tissue forms a conjugate which will produce a state of sensitization in animals. Analysis by electrophoretic process demonstrates that this conjugate may be formed in the skin of the living animal. It is possible to obtain cross-precipitation reactions between antiserum from animals sensitized by conjugates with the same haptens and different proteins. Attempts to produce this result using the same protein and different haptens fail. At time it has been possible to produce a precipitate using only the unconjugated hapten and antiserum. This phenomenon may explain the immediate types of drug reactions. In some instances the addition of hapten to antiserum results in no precipitation but blocks precipitate formation on subsequent addition of a normally reacting conjugate. The conjugate yields a precipitate with the antiserum if hapten is not added first. The failure of an unconjugated hapten to cause a precipitate is due to serologic univalence of the hapten.[15] This is in keeping with the "lattice" theory of antigen-antibody precipitate formation which states that a lattice is formed by increasing numbers of specifically linked antigen-antibody complexes. Each antigen molecule in the complex is linked to two or more antibody molecules and each antibody molecule to two or more antigen molecules. This mass or "lattice" increases until a critical level is reached and a precipitate is formed.

Guinea pigs sensitized by repeated intradermal injections of hapten will demonstrate delayed skin reactions when challenged with hapten alone, but an immediate anaphylactic reaction occurs when challenged by hapten-protein conjugate. By the application of this principle, it has been possible to desensitize animals by injection of haptens. This has been much easier to do in the Schultz-Dale preparation than in the live animal. Desensitization in man by haptens has been unsuccessful.

Haptens are capable of cross-reactions. The closer the chemical relationship, the stronger is the cross-reaction. At times the cross-reactor may give a stronger reaction than the original hapten. In a series of closely related halo- and nitrobenzene compounds there is a close correlation between their ability to sensitize and their ability to combine with aniline. A correlation between ability to sensitize and ability to cause mitosis and necrosis of cells in culture has also been demonstrated with a series of 1, 2, 4 dinitrochlorbenzenes.[59]

Hapten conjugation may well explain drug reactions. From animal experiments one may conclude that: (1) hapten-protein conjugates formed in vivo generally give delayed allergic reactions and less frequently immediate type allergic reactions; (2) conjugates formed in vitro chiefly produce immediate or anaphylactic type reactions. How-

ever, the latter may be converted into the delayed type of reaction by prior intraperitoneal injection of an adjunct such as killed tubercle bacilli. Mayer[74] has explained the action of adjuncts by postulating that the cellular antibody of the delayed type of sensitization is formed in response to the union of antigen with fibroid proteins, whereas the immediate types are produced by antigen with globular proteins. Favour[28] stated that "there is considerable evidence to show that the selective sites of cellular uptake of haptens or antigenic substance have a great deal to do with the patterns of subsequent allergic reactions that may follow." For example, antigen demonstrated by fluorescent technique to be present in the vascular wall is the primary site of both mild and severe anaphylactic pathologic manifestations.

Investigators have understandably been handicapped by an inability and disinclination to use humans for experimental studies. In most instances of drug allergy there are no demonstrable humoral antibodies. This leaves reproduction of reactions as the only available means of demonstrating drug allergy. This is usually extremely hazardous. In 1949, Lawrence[60] demonstrated the passive transfer of delayed tuberculin skin sensitivity by injecting intradermally viable leukocytes from a tuberculin-positive subject into a tuberculin-negative individual. This is a transient phenomenon which is dependent on the intensity of reaction in the tuberculin-positive subject and the number of leukocytes injected. Similar passive transfer tests with other substances, particularly drugs causing delayed skin reaction, have been successfully performed.[15] This may prove to be a feasible method for demonstrating drug allergy in humans.

Haxthausen[50] studied delayed allergy of the contact dermatitis type in identical twins. He sensitized one to picryl chloride. After a suitable interval he transplanted skin from each of the twins to the other one. He then retested for sensitivity to picryl chloride and found that the skin from the sensitized subject now growing on the nonsensitized twin no longer showed reaction to picryl chloride; whereas the skin taken from the nonsensitive donor reacted just as the rest of the skin of the sensitive recipient. Others have shown that general sensitization can be attained by treatment of small skin islands that were completely isolated by incision through the skin as long as the lymphatics on the skin muscle were intact.[59] Hauxthausen[49] has also demonstrated that he could inhibit skin sensitization to dinitrochlorobenzene by applying ethyl chloride and "freezing" the skin as late as 8 days after application of the sensitizing substance. It is difficult to understand the relatively long time factor in this observation. Indeed, none of the foregoing observations in humans can be satisfactorily explained at present. They are mentioned here because they may be significant additions to our knowledge of delayed sensitivity and drug allergy.

Drugs with high molecular weights such as heterologous sera, hormones, and other proteins are antigenic without further combination or hapten conjugation. They may cause either delayed or immediate allergic reactions.

Another group of drug reactions that is not completely explained by hapten-protein conjugation is that exemplified by "Sedormid purpura" described originally by Ackroyd.[2] The serum of a patient with Sedormid-induced purpura, when combined with Sedormid, a sedative drug used in Europe, and platelets either from the patient or a normal subject, produced agglutination and subsequent lysis of platelets. Bigelow[13] demonstrated this also with quinidine and quinine purpuras. In none of these instances were there demonstrable skin reactions. Similarly, Moeschlin and Wagner[80] showed that the serum of patients with agranulocytosis due to aminopyrine (Pyramidon) would agglutinate leukocytes from the patient or from a normal subject in vitro, if the serum contained aminopyrine. In previously mentioned purpuric reactions the drug may be added in vitro, but in amidopyrine agranulocytosis it must be given to the patient at least 3 hours before the serum is drawn. The most likely explanation for these phenomena is

the attachment of the drug to the surface of the cell which then combines with antibody in the serum to cause agglutination and lysis.

In cutaneous hemorrhagic lesions of drug allergy, Rostenberg[93] believes that the probable mechanism is similar to that of the nonspecific Shwartzman phenomenon. Shwartzman in 1928 described primary sensitization of the skin by intracutaneous injection of an antigen. After a suitable interval certain substances such as autolysis-free bacterial filtrates were administered intravenously to the test animal. Areas of hemorrhage and even necrosis appeared at the site of the preparatory injection. This reaction is nonspecific, because the eliciting material does not have to be the same as that used in the intracutaneous injection.

Another possible mechanism in drug allergy is the familiar Jarisch-Herxheimer reaction. It is postulated that the drug may release a toxic or sensitizing agent from the infecting organism or body tissues to set up allergic reactions in the patient. Some drugs may produce allergic types of reactions through the release of histamine from normal tissue without previous sensitization.[63]

Space does not allow us to discuss the various theories that attempt to explain what occurs following the antigen-antibody reaction. Today this is a very exciting field of study among allergists and immunologists. The reader is referred to the standard texts of allergy and immunology and more specifically to such articles as concern themselves with the enzymatic theories,[19, 42, 97, 104] older chemical theories,[105] and the most recent reports on physicochemical and biochemical aspects of hypersensitivity.[61, 86]

SUMMARY AND CONCLUSION

This review calls to the attention of the pediatrician the ever-increasing incidence and importance of drug allergy. The terminology used to describe various drug reactions has been clarified. The mechanisms which explain drug allergy at this time have been discussed and the manifestations that they elicit have been described. Some of the more commonly used drugs and the reactions they produce were mentioned. The tests for drug allergy, together with its prevention and treatment, were stressed.

The reproduction of allergic manifestations by administration of the suspected offending drug is not recommended.

There is a need for more and better reporting of allergic reactions to drugs,[18, 62, 93] so that the practitioner will have this information readily available. Finally, the number of serious hypersensitivity reactions to drugs would be considerably reduced if on each occasion, before medication is given, the physician would ask himself, "Does the necessity for administering this drug warrant the risks involved, including possible sensitization?"

REFERENCES

1. A. M. A. Council on Drugs: Report on New and Nonofficial Drugs, J. A. M. A. **168:** 1771, 1958.
2. Ackroyd, J. F.: The Cause of Thrombocytopenia in Sedormid Purpura, Clin. Sc. **8:** 269, 1949.
3. Alexander, H. L.: Reactions With Drug Therapy, Philadelphia, 1955, W. B. Saunders Company.
4. Allen, H. S., Jr., Beacham, E. G., and Keschner, H. W.: Hepatitis and Hypokalemia in Tuberculosis, Am. Rev. Tuberc. **68:** 136, 1953.
5. Alving, A. S., Kellermeyer, R. W., Tarlov, A., Schrier, S., and Carson, P. E.: Biochemical and Genetic Aspects of Primaquine-Sensitive Hemolytic Anemia, Ann. Int. Med. **49:** 240, 1958.
6. Arkins, J. A., Ruetz, P. P., and Squier, T. L.: Mephenesin (Tolserol) Sensitivity With Demonstrable Skin-Sensitizing Antibody in the Serum, J. Allergy **28:** 247, 1957.
7. Baer, R. L., Serri, F., and Vial-Weissenbach, C.: Studies on Allergic Sensitization to Certain Topical Therapeutic Agents, A. M. A. Arch. Dermat. **71:** 19, 1955.
8. Becker, R. M.: Effect of Penicillinase on Circulating Penicillin, New England J. Med. **254:** 952, 1956.
9. Bell, R. C.: Anaphylactic Shock Due to Oral Penicillin, Lancet **2:** 439, 1956.
10. Berkowitz, M., Glaser, J., and Johnstone, D.: Incidence of Allergy to Drugs in Pediatric Practice, Ann. Allergy **11:** 561, 1953.
11. Bierlein, K. J.: Repeated Anaphylactic Reactions in a Patient Highly Sensitized to Penicillin, Ann. Allergy **14:** 35, 1956.

12. Bierly, M. Z.: Considerations of Special Interest to the Allergist on the Composition and Production of Poliomyelitis Vaccine, Ann. Allergy **14:** 349, 1956.
13. Bigelow, F. S., and Desforges, J. F.: Platelet Agglutination by an Abnormal Plasma Factor in Thrombocytopenic Purpura Associated With Quinidine Ingestion, Am. J. M. Sc. **224:** 274, 1952.
14. Blue, J. A.: An Evaluation of Histamine as a Therapeutic Agent in Some Allergic Disorders, South. M. J. **49:** 636, 1956.
15. Boyd, W. C.: Fundamentals of Immunology, ed. 3, New York, 1956, Interscience Publishers.
16. Bridges, R. A., Berendes, H., and Good, R. A.: Serious Reactions to Novobiocin, J. Pediat. **50:** 579, 1957.
17. Brown, E. A.: The General Practitioner and Drug Reactions, GP **13:** 92, 1956.
18. Brown, E. A.: The Reporting of Drug Toxicity, Ann. Allergy **14:** 206, 1956.
19. Burdon, K. L.: Enzyme Activation in Allergic Reactions, Ann. Allergy **16:** 168, 1958.
20. Bureau of Medicine, Food and Drug Administration, U. S. Department of Health, Education and Welfare: Safe New Drugs, Pamphlet Publ., 1958.
21. Carr, E. A.: Drug Allergy, Pharmacol. Rev. **6:** 365, 1954.
22. Chapman, John, S.: Personal communication.
23. Chase, M. W.: Inheritance in Guinea Pigs of the Susceptibility to Skin Sensitization With Simple Chemical Compounds, J. Exper. Med. **73:** 711, 1941.
24. Collins-Williams, C., and Vincent, J.: Sensitivity Reactions to Penicillin in Children, Ann. Allergy **11:** 454, 1953.
25. Crepea, S. B.: Allergy (asthma) to Monkey Protein in Poliomyelitis Vaccine, J. Allergy **28:** 262, 1957.
26. Danhof, I. E.: Factors in the Etiology of Chlorpromazine Jaundice: an Experimental Study, Texas Rep. Biol. & Med. **16:** 443, 1958.
27. Eisalo, A., Leskenen, O., and Oka, M.: Fatal Anaphylactic Shock Following Corticotrophin, Acta med. scandinav. **155:** 1, 1956.
28. Favour, C. B.: In Vitro Studies on Cell Injury in the Tuberculin-Type Reaction: Implications in Homotransplantation, Ann. New York Acad. Sc. **64:** 842, 1957.
29. Fein, B. T., and Criep, L. H.: Exfoliative Dermatitis From Dihydrostreptomycin. Texas J. Med. **46:** 712, 1950.
30. Fein, B. T.: Letters of the Int. Cor. Soc. of Allergists **21:** 183, 1958.
31. Feinberg, S. M., and Feinberg, A. R.: Allergy to Penicillin, J. A. M. A. **160:** 778, 1956.
32. Feinberg, A. R., and Malkiel, S.: Aspirin Sensitivity-Experimental Studies, J. Allergy **22:** 75, 1951.
33. Feinberg, S. M., Malkiel, S., and Feinberg, A. R.: The Antihistamines, Chicago, 1950, The Year Book Publishers, Inc.
34. Felix, N. S.: Chloramphenical: Applied Pharmacology, Pediat. Clin. North America, **3:** 317, 1956.
35. Fisher, A. A., and Sturm, H. M.: Procaine Sensitivity: The Relationship of the Allergic Eczematous Contact-Type to the Urticarical, Anaphylactoid Variety; The Use of Xylocaine in Procaine-Sensitive Individuals, Ann. Allergy **16:** 593, 1958.
36. Friedlaender, S.: Penicillinase in the Treatment of Allergic Reactions to Penicillin, J. Allergy **30:** 181, 1959.
37. Friedman, H. T.: Letters of the Int. Cor. Soc. of Allergists **21:** 183, 1958.
38. Gangarosa, E. J., Landerman, N. S., Rosch, P. J., and Hendon, E. G., Jr.: Hematologic Complications Arising During Ristocetin Therapy, New England J. Med. **259:** 156, 1958.
39. Getzoff, P. H.: The Use of Antihistamine Drug Prophylaxis Against Diodrast Reactions, J. Urol. **65:** 1139, 1951.
40. Gitlin, D., Gross, P. A. M., and Janeway, C. A.: The Gamma Globulins and Their Clinical Significance: I. Chemistry, Immunology and Metabolism, New England J. Med. **260:** 21, 1959.
41. Glaser, J.: Allergy in Childhood, Springfield, Ill., 1956, Charles C Thomas, Publisher.
42. Godlowski, Z. Z.: The Enzymatic Concept of Anaphylaxis and Allergy, Baltimore, 1953, Williams & Wilkins Company.
43. Goodman, L. S., and Gilman, A.: The Pharmacologic Basis of Therapeutics, New York, 1955, The Macmillan Company.
44. Gould, J. C.: Environmental Penicillin and Penicillin-Resistant Staphylococcus Aureus, Lancet **1:** 489, 1958.
45. Grant-Peterkin, G. A.: Drug Eruptions, Brit. J. Clin. Pract. **10:** 657, 1956.
46. Gropper, A. L.: Diphenylhydantoin Sensitivity, New England J. Med. **254:** 522, 1956.
47. Haensch, R.: An Intense Antigen-Antibody Reaction Induced by Periston and the Finding of Auto-Antibodies in Erythrodermia, Ärztl. Wchnschr. **12:** 824, 1957.
48. Halpern, S. R., and Halpern, D.: Reactions From DPT Immunization and Its Relationship to Allergic Children, J. PEDIAT. **47:** 60, 1955.
49. Haxthausen, H.: Some Problems Concerning the Pathogenesis of Allergic Eczemas, Elucidated by Experiments on Sensitization With Dinitrochlorobenzene, Acta dermatvenereol. **20:** 257, 1939.
50. Haxthausen, H.: The Pathogenesis of Allergic Eczema Elucidated by Transplantation Experiments on Identical Twins, Acta dermat.-venereol. **23:** 438, 1943.
51. Henley, E. E., McPhaul, J. J., and Albert, S. N.: Anaphylactic Reactions to Dextran: Report of a Case, M. Ann. District of Columbia **27:** 21, 1958.
52. Hollister, L. E.: Allergy to Chlorproma-

zine—Manifested by Jaundice, Am. J. Med. **23:** 870, 1957.
53. Hyman, A. L.: Anaphylactic Shock After Therapy With Penicillinase, J. A. M. A. **169:** 593, 1959.
54. James, H. D., and Stanton, J. P.: Skin Manifestations of Drug Allergy, Postgraduate Med. **21:** 485, 1957.
55. Keefer, C. S., and Hewitt, W. L.: The Therapeutic Value of Streptomycin: a Study of 3000 Cases, Ann Arbor, 1948, J. W. Edwards.
56. Keeney, E. L., Weiss, H. A., and Mohr, C. F.: The Use of Cortisone or ACTH During Rapid Desensitization of Allergic Patients, J. Allergy **26:** 141, 1955.
57. King, H., and Karelitz, S.: Streptomycin and Dihydrostreptomycin; Applied Pharmacology, Pediat. Clin. North America **3:** 279-294, 1956.
58. Klotz, S. D., and Bernstein, C.: Allergy to Meprobamate With Some Observation Regarding the Tranquilizing Drugs, South. M. J. **50:** 1478, 1957.
59. Landsteiner, K.: The Specificity of Serological Reactions, Cambridge, 1945, Harvard University Press.
60. Lawrence, H. S.: The Cellular Transfer of Cutaneous Hypersensitivity to Tuberculin in Man, Proc. Soc. Exper. Biol. & Med. **71:** 516, 1949.
61. Lawrence, H. S., editor: Cellular and Humoral Aspects of the Hypersensitivity States, New York, 1959, Paul B. Hoeber, Inc.
62. Leake, C. D.: Drug Allergies, Postgraduate Med. **17:** 132, 1955.
63. Lecomte, J.: Drug Reactions Linked With Histamine Release in Man, in Rosenheim, M. L., and Moulton, R., editors: Sensitivity Reactions to Drugs, Springfield, Ill., 1958, Charles C Thomas, Publisher.
64. Lehr, D.: Lowered Incidence of Sensitization Through Use of Sulphonamide Combinations; A New Concept, Brit. M. J. **2:** 543, 1948.
65. Leider, M.: Practical Pediatric Dermatology, St. Louis, 1956, The C. V. Mosby Company.
66. Levan, M. E.: Chlorpromazine Dermatitis; Occupational and Immunochemical Aspects, New England J. M. **256:** 651, 1957.
67. Lowell, F. C.: Allergic Reactions to Drugs, Practitioner, **178:** 673, 1957.
68. Lowell, F. C.: Allergic Reactions to Sulfonamide and Antibiotic Drugs, Ann. Int. Med. **43:** 333, 1955.
69. Maganzini, H. C.: Anaphylactoid Reaction to Penicillins V and G Administered Orally; Report of Two Cases and Brief Review of the Subject, New England J. Med. **256:** 52, 1957.
70. Matheson, A., and Elegant, L.: Penicillin Reactions in Children; Study of the Value of the Skin Test in Penicillin Sensitization, J. Allergy **26:** 415, 1955.
71. Matsaniotis, N., Jacobs, J., and Smith, M. H. D.: Hypersensitivity Reactions Associated With Sodium Para-aminosalicylate Therapy; Four Case Reports and Review of the Literature, Pediatrics **21:** 781, 1958.
72. Mathews, K. P., Hemphill, F. M., Lovell, R. G., Forsythe, W. E., and Sheldon, J. M.: A Controlled Study on the Use of Parenteral and Oral Antihistamines in Preventing Penicillin Reactions, J. Allergy **27:** 1, 1956.
73. Mayer, R. L.: Shortcomings of the Experimental Methods for Detection of Sensitizing Properties of New Drugs, J. Allergy **26:** 133, 1955.
74. Mayer, R. L.: The Role of the Carrier in the Formation of Complete Antigens, J. Allergy **28:** 191, 1957.
75. McCombs, R. P., Patterson, J. F., and MacMahon, H. E.: Syndromes Associated With Allergic Vasculitis, New England J. Med. **255:** 251, 1956.
76. McLean, C. C.: Penicillin in Fluid Milk, Arch. Pediatrics **73:** 276, 1956.
77. McLetchie, N. G. B., MacDonald, R. M., and Cutts, J. H.: Polyarteritis Nodosa. Report of a Case With Proof of Drug Allergy, Canad. M. J. **76:** 213, 1957.
78. Mechanic, R. C., and Meyers, L.: Chlorpromazine-Type Cholangitis; Report of a Case Occurring After the Administration of Prochlorperazine, New England J. Med. **259:** 778, 1958.
79. Minno, A. M., and Davis, G. M.: Penicillinase in the Treatment of Penicillin Reactions, J. A. M. A. **165:** 222, 1957.
80. Moeschlin, S., and Wagner, K.: Agranulocytosis Due to the Occurrence of Leukocyte-Agglutinins, Acta haemat. **8:** 29, 1952.
81. Motulsky, A. G.: Drug Reactions, Enzymes and Biochemical Genetics, J. A. M. A. **165:** 835, 1957.
82. Nelson, W.: Textbook of Pediatrics, ed. 6, Philadelphia, 1954, W. B. Saunders Company, p. 1200.
83. Nichols, M. N.: Insulin Allergy, J. PEDIAT. **46:** 314, 1955.
84. Parke, Davis & Company: Clinical Report on Chloromycetin® in the Treatment of Premature and Newborn Infants. Letter distributed to doctors in January, 1959.
85. Payne, R.: Leukocyte Agglutinins in Human Sera, Arch. Int. Med. **99:** 587, 1957.
86. Proceedings of the Third Internat. Congr. of Allergology, Paris, 1958, Éditions Médicales Flammarion.
87. Rajka, G., and Vincze, E.: Penicillin Combined With Gamma Globulin as a Diagnostic Agent in Urticaria of the Serum-Sickness Type Due to Penicillin, Ann. Allergy **16:** 662, 1958.
88. Ratner, B., Crawford, L. V., Feldman, R., and Krimli, A.: Mechanism and Evolution of Sensitization With Particular Reference to the Delayed Allergic Reaction, Ann. Allergy **16:** 662, 1958.
89. Rich, A. R.: Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hop-

kins Hosp. **71:** 123, 1940.
90. Rich, A. R.: Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **77:** 43, 1945.
91. Rosenblum, A. R.: Anaphylactic Reaction to D. P. T. Vaccine Caused by a Silk Antigen, Ann. Allergy **15:** 621, 1957.
92. Rosenthal, A.: Eight Anaphylactic Reactions to Penicillin, New York J. Med. **54:** 1485, 1954.
93. Rostenberg, A., and Webster, J. R.: Mechanisms of Cutaneous Drug Reactions, Especially to Antibiotics, J. A. M. A. **154:** 221, 1954.
94. Rubens, E.: Local Hemorrhagic-Necrotic Skin Reaction Following Penicillin, J. PEDIAT. **38:** 630, 1951.
95. Scott, J. L., Cartwright, G. E., and Wintrobe, M. M.: Acquired Aplastic Anemia: an Analysis of Thirty-nine Cases and Review of the Pertinent Literature, Medicine **38:** 119, 1959.
96. Seltzer, A.: A Useful Device for Treating Acute Allergic Drug Reactions, the Medihaler-Epi, M. Ann. District of Columbia **27:** 131, 1958.
97. Sevag, M. G.: A New Theory of Allergic Phenomena, Ann. Allergy **14:** 233, 1956.
98. Shaw, E. B., Dermott, R. V., Lee, R., and Burbridge, T. N.: Phenothiazine Tranquilizers as a Cause of Severe Seizures, Pediatrics **23:** 485, 1959.
99. Sherman, W. B.: Drug Allergy, J. A. M. A. **140:** 447, 1949.
100. Sherman, W. B., and Kessler, W. R.: Allergy in Pediatric Practice, St. Louis, 1957, The C. V. Mosby Company.
101. Simon, S. W.: Skin Sensitivity to Streptomycin, J. Allergy **21:** 400, 1950.
102. Smith, V. M.: Fatal Reactions to Penicillin—Evaluation of a Test for Sensitivity, New England J. Med. **257:** 447, 1957.
103. Spain, W. C., and Fontana, V. J.: Allergic Accidents Resulting From Therapeutic Agents, GP **14:** 113, 1956.
104. Ungar, G., and Hayashi, H.: Enzymatic Mechanisms in Allergy, Ann. Allergy **16:** 542, 1958.
105. Urbach, E., and Gottlieb, P. M.: Allergy, New York, 1943, Grune & Stratton.
106. Vaughan, W. T., and Black, J. H.: Practice of Allergy, ed. 3, St. Louis, 1954, The C. V. Mosby Company.
107. Walsh, J. J., Linn, R. H., and Derbes, V. J.: Pyrexia Due to Isonicotinic Acid Hydrazide, J. Allergy **27:** 548, 1956.
108. Welch, H., Braley, et al.: Principles and Practice of Antibiotic Therapy, New York, 1954, Medical Encyclopedia, Inc.
109. White, P.: Juvenile Diabetes Mellitus, in Brenneman's Practice of Pediatrics, Hagerstown, Md., 1947, W. F. Prior, vol. 3, chap. 12.
110. Willcox, R. R., and Fryers, G. R.: Sensitivity to Repository Penicillins, Brit. J. Ven. Dis. **33:** 209, 1957.
111. Yow, E. M.: A Re-evaluation of Sulfonamide Therapy, Ann. Int. Med. **43:** 323, 1955.
112. Zimmerman, M. C.: Penicillinase-Proved Allergy to Penicillin in Poliomyelitis Vaccine, J. A. M. A. **167:** 1807, 1958.
113. Zinkham, W. H.: An In-Vitro Abnormality of Glutathione Metabolism in Erythrocytes From Normal Newborns: Mechanism and Clinical Significance, Pediatrics **23:** 18, 1959.
114. Ziprikowski, L., and Glazer, I.: Dermatitis Medicamentosa Apparently Due to Tetracycline, J. Allergy **29:** 336, 1958.
115. Zucker, A., and Florio, A.: Allergy to Proteins Derived From Animal Sources as Seen in Immunization Procedures, Ann. Allergy **16:** 413, 1958.

Severe myocarditis with recovery in a child with visceral larva migrans

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IN 1947 Perlingiero and Gyorgy[1] described a new clinical syndrome characterized by fever, hepatomegaly, leukocytosis with marked eosinophilia, and hyperglobulinemia. The pathological findings in this syndrome were reported in 1949 by Zuelzer and Apt.[2] In 1952 Beaver and associates[3] demonstrated that these pathological changes resulted from a parasitic infection with the larval form of a nematode commonly found in dogs *(Toxocara canis)* and cats *(Toxocara cati)*, and suggested the name visceral larva migrans. Karpinski, Evert-Suarez, and Sawitz[4] later introduced the term larval granulomatosis. Approximately 40 instances of this syndrome have been reported to date, almost exclusively in the "toddler" age group.

The ova of this parasite are passed in the feces of infected dogs or cats and contaminate the soil. Under favorable circumstances of temperature and humidity, the ova may become embryonated and, if ingested, pass through the stomach of the human host and hatch in the small intestine. The larvae penetrate the intestinal wall and migrate via the blood stream or lymph passages to the liver, lungs, and other organs. The life cycle is not completed in man who is an accidental host. The parasites remain in the invaded tissues in the larval stage, and may be viable in the human host for a year or more.[5] They have been detected in the liver,[4] lungs,[6] brain,[7] heart,[8] and eyes.[9]

The basic pathologic alteration which results from the presence of toxocara larvae in human tissues is the formation of eosinophilic granulomas. These are most commonly found in the liver; the lungs are also frequently involved. A marked eosinophilia in the bone marrow and peripheral blood is a consistent finding.

The presence of the larvae of *Toxocara canis* in the myocardium of a patient who died as a result of overwhelming generalized infection with the parasite has been reported in one autopsy protocol.[8] Necrotic, granulomatous foci associated with eosinophilic infiltration in the myocardium have also been reported to occur in visceral larva migrans by Brill and associates.[6]

A 2 7/12-year-old Negro female was recently encountered with clinical and laboratory evidence of visceral larva migrans. Severe myocarditis manifested by cardiac en-

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largement and congestive heart failure was observed during the acute phase of the parasitic infection. The cardiac manifestations in this patient probably resulted from direct invasion of the myocardium by the parasites. It is the purpose of this report to describe the clinical and laboratory findings in this child who made a complete recovery and to discuss briefly the problems encountered in the management of this variety of heart disease. No previous clinical reports of myocardial involvement due to *Toxocara canis* with recovery are known to us.

CASE REPORT

E. D., a Negro female, was $2\frac{7}{12}$ years of age when first admitted to The Children's Hospital of Philadelphia on June 26, 1956. She was transferred from a hospital in Chester County, Pennsylvania, to which she had been admitted 3 months previously with evidence of cardiac failure, bilateral pneumonitis, and anemia. She had responded initially to treatment with digitalis, antibiotics, and oxygen, but the degree of hepatomegaly and cardiomegaly did not regress with the disappearance of other evidences of congestive heart failure. She was transferred, therefore, to The Children's Hospital of Philadelphia for further diagnostic study.

Past medical history. This was significant only in that the patient was known to eat soil from the family yard where she played frequently with a pet dog. Subsequently it was demonstrated that the stools from this dog contained the ova of the parasite *Toxocara canis*. The family history was unremarkable. There were three healthy siblings all considerably older than the patient.

Physical examination. On admission a pleasant, cooperative Negro female child with no respiratory distress or cyanosis was observed. The respiratory rate was 24 per minute; pulse rate, 120 per minute; blood pressure, 80/50 (right arm) and 108/70 (right leg); temperature, 36.7° C. A fine papular rash was present on the anterior trunk and extremities. Several enlarged anterior and posterior cervical lymph nodes were palpable. Auscultation of the lungs revealed bilateral ronchi. There was a persistent cough productive of thick secretions. The heart was enlarged to percussion; the apex beat was in the sixth left intercostal space in the anterior axillary line. The heart sounds were muffled; no cardiac murmurs were audible. The liver edge was palpable 5 cm. below the right costal margin; the spleen was not palpable; generalized lymphadenopathy was present. The remainder of the physical examination was negative.

Laboratory findings. Multiple urinalyses demonstrated no abnormalities. The blood count on admission disclosed a hemoglobin level of 10.3 Gm. per cent with 3.44 million red blood cells. The white blood cell count was 17,000 with 21 per cent neutrophils, 42 per cent lymphocytes, and 37 per cent eosinophils. The high eosinophilic count was confirmed and persisted until 3 weeks after admission, at which time the white cell count was 12,500 with 72 per cent neutrophils, 25 per cent lymphocytes, and 6 per cent eosinophils. Cultures of the throat and nasopharynx revealed no significant organisms. The sedimentation rate on admission was 27 mm. per hour by the Cutler method. The total serum proteins were 8.3 Gm. per cent with albumin, 3.3 Gm. per cent, and globulin, 5.0 Gm. per cent.

Examinations of the patient's stools for ova and parasites were negative on three occasions. Nasal and rectal smears demonstrated no eosinophils. A trichinosis precipitin test, a trichinosis skin test, and a serological test for syphilis were negative.

An electrocardiogram was recorded on admission and revealed only a sinus tachycardia. There was no axis deviation in the limb leads. In the precordial leads the QRS complexes had a left-sided, adult-type configuration. There were no definite T-wave or S-T segment changes.

Roentgenographic examination of the chest on admission (Fig. 1, *A*) demonstrated a marked degree of cardiac enlargement of a generalized nature. The pulmonary vascular markings were within normal limits.

A lymph node biopsy was reported to show only chronic active lymphadenitis of a

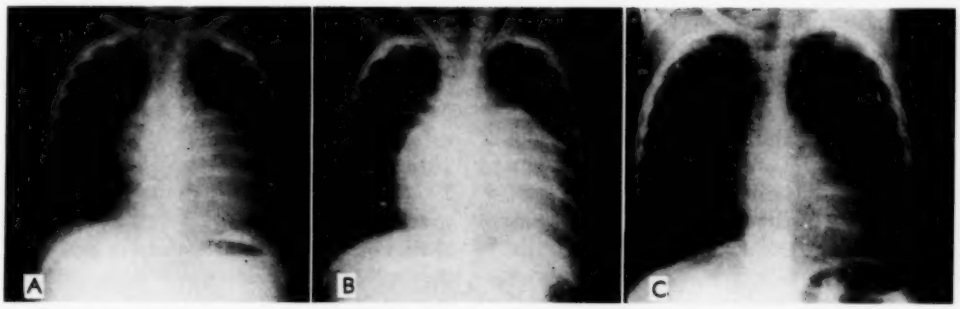

Fig. 1. *A*, Roentgenogram in anteroposterior view of a $2\frac{7}{12}$-year-old Negro girl in June, 1956, at the time of first admission for visceral larva migrans. Massive cardiac enlargement of a diffuse nature is evident. *B*, An even greater degree of cardiac enlargement is seen in this film taken 5 months later at the time of the second hospital admission when overt evidence of congestive heart failure was present. *C*, Roentgenogram in April, 1959, demonstrating cardiac silhouette of normal size, shape, and position.

nonspecific nature. A liver biopsy was not performed.

Hospital course. During the first two weeks of hospitalization, the patient was asymptomatic and afebrile. On the nineteenth hospital day severe respiratory distress developed abruptly. The respiratory rate was 80 per minute; cardiac rate, 130 per minute; temperature, 37.8° C. Oxygen, antibiotics, and cortisone therapy (100 mg. per day) were started. A roentgenogram of the chest demonstrated pneumonitis and atelectasis involving the right lower lobe. The patient appeared critically ill but gradual improvement began on the following day. Serial roentgenograms of the chest showed progressive improvement in the pulmonary findings, but the enlarged cardiac silhouette remained unchanged.

Several days after the beginning of cortisone therapy, marked abdominal distention was noted. The liver edge was still palpable 5 cm. below the right costal margin; the spleen was not palpable. When the cortisone dosage was tapered, the liver became smaller but the edge was still palpable at the time of discharge. Complete bed rest and oral iron medication were recommended when the patient was discharged to home care on Aug. 3, 1956.

One month thereafter the patient was brought to the Medical Out-Patient Department. She was reported to be doing well and her physical examination was unchanged. At a second visit 3 months later, the patient was found to be acutely ill with marked respiratory distress, tachycardia, and edema; immediate admission was arranged. During the interval at home, the patient had continued to eat soil from the ground in the yard where she played with her pet dog.

Physical examination at the time of the second admission revealed a very irritable, dyspneic, and orthopneic child. The respiratory rate was 48 per minute; pulse rate, 144 per minute; blood pressure, 100/60 (right arm); and temperature, 36.8° C. The chest was emphysematous with a slight left precordial bulge. The apex beat was in the anterior axillary line; a gallop rhythm was audible over the entire precordium. The cardiac sounds were of poor quality. No cardiac murmurs were audible. The liver edge was palpable 10 cm. below the right costal margin; the spleen was not palpable. Auscultation of the lungs revealed scattered ronchi. There was a small amount of edema in the periorbital regions.

Acute congestive failure was diagnosed and the patient was started on oxygen therapy, digitalis, a low-salt diet, and mercurial diuretics. Her response to this regimen was very favorable and in a few days she was remarkably improved. One month later she

developed another episode of acute respiratory distress with moist râles and dullness over the left chest. A diagnosis of pneumonitis was again confirmed by roentgenographic studies. She was started on cortisone therapy (75 mg. per day) and became asymptomatic within a few days.

Laboratory findings. At the time of the second admission the urinalysis was abnormal, and included a trace of protein, 8 to 9 red blood cells and 25 to 30 white blood cells per high-power field. These abnormalities disappeared with clearing of the congestive heart failure. The blood count showed a hemoglobin level of 12 Gm. per cent with 4.1 million red blood cells; the white blood cell count was 12,000 with 40 per cent neutrophils, 54 per cent lymphocytes, and 6 per cent eosinophils. Four days later the absolute eosinophil count was 3,443 per cubic millimeter. Forty days later the white blood cell count was 14,000 with 38 per cent eosinophils. The total serum proteins were 6.9 Gm. per cent with albumin, 2.6 Gm. per cent, and globulin, 4.4 Gm. per cent. Repeated stool examinations were again negative for ova and parasites. The electrocardiogram revealed no definite abnormalities. Fig. 1, *B* demonstrates the massive enlargement of the cardiac silhouette present at the time of the second hospital admission.

Subsequent course. In December, 1956, after 7 weeks of hospitalization, the patient was transferred to The Atlantic City Seashore Home for convalescent care with the intent of separating the patient from the source of her parasitic infection. After one month in the convalescent institution, the cortisone therapy was gradually decreased and finally discontinued. A generalized rash associated with high fever and stomatitis developed on the last day of cortisone administration. Antibiotic therapy was restarted and the symptoms regressed slowly over a period of several days. The remainder of the patient's stay at the convalescent institution was uneventful. There were no further febrile episodes or any evidence of congestive heart failure. Six months after admission she was discharged to be followed in the Cardiac Clinic of The Children's Hospital of Philadelphia.

Examinations in December, 1957, and June, 1958, failed to reveal a heart murmur or any evidence of cardiac dysfunction. The patient was reported to be in good health. Fluoroscopic examinations indicated progressive decrease in cardiac size.

At the most recent examination in February, 1959, the patient was 5 years old. She was again reported to be completely asymptomatic; her physical growth and development were within the normal range. Pica was no longer a complaint. The dog infected with *Toxocara canis* has been removed from the household. Studies at this visit included a normal white blood cell and differential count in which only 1 per cent eosinophils were found. The electrocardiogram was entirely normal. A chest film (Fig. 1, *C*) demonstrated a return of the heart to normal size. On physical examination, no heart murmurs were audible; the liver and spleen were not palpable. The only persisting abnormal finding was the electrophoretogram which revealed the following levels: total proteins, 6.7 Gm. per cent; albumin, 2.7 Gm. per cent; globulin, 4.0 Gm. per cent. The albumin/globulin ratio was 0.67 with alpha$_1$ globulin, 0.5 Gm. per cent; alpha$_2$ globulin, 1.0 Gm. per cent; beta globulin, 0.7 Gm. per cent; and gamma globulin, 1.8 Gm. per cent.

DISCUSSION

The diagnosis of visceral larva migrans can be established during life with absolute certainty only by the finding of granulomatous lesions in a liver biopsy containing identifiable larval forms of the Toxocara parasite. Although this confirmation is not available in our patient, the clinical and laboratory evidence in favor of the diagnosis is quite convincing. The age of the patient, the history of pica, and the finding of *Toxocara canis* ova in the stool specimens obtained from the family dog provide the precise conditions necessary for infection. Fever, hepatomegaly, and repeated episodes of bronchitis and/or pneumonia are common

symptomatic features of the disease and were prominent clinical findings in our patient. Leukocytosis with a marked eosinophilia and hyperglobulinemia are the classical laboratory findings and were present in this patient. The persistence of an abnormal electrophoretic pattern of the serum proteins for several years after the initial infection is also a consistent finding. The favorable response of the patient to separation from the source of infection is evidence in favor of visceral larva migrans. In addition, stool examinations, skin tests, and biopsy studies of muscle and lymph nodes failed to reveal any other variety of parasitic infection.

Involvement of the myocardium has been reported in a number of parasitic diseases: amebiasis, trypanosomiasis (Chagas disease), trichinosis, strongyloidosis, schistosomiasis, heterophyiasis, cysticercosis, and echinococcosis. Direct invasion of the myocardium by the larva of *Toxocara canis* has been observed at autopsy in a child who died of this disease. That direct invasion of the myocardium by the *Toxocara canis* larvae occurred in our patient also seems quite likely. In the absence of significant cardiac murmurs and hypertension, massive cardiac enlargement and profound congestive heart failure with recovery are indicative of myocarditis. The deterioration of the cardiac status of our patient with re-exposure to the offending parasite may indicate that the *Toxocara canis* larvae rather than a coincidental viral or other etiological agent were responsible for the myocarditis. Since visceral larva migrans is an endemic disease in many parts of the United States, this parasitic etiology must henceforth be considered in young patients with myocarditis of obscure origin.

The fundamental therapeutic measure in our patient consisted in separating her from the source of infection, namely, the soil contaminated by the family dog. Failure to carry out this simple procedure following the initial admission, and the inability of the parents to interfere with the patient's ingestion of parasite-containing soil resulted in a relapse. A 6 months' period of separation from the source of infection was followed by marked improvement in the patient's general as well as cardiac status. Pica is also less likely to occur in mentally normal children beyond the age of 3 years.

The symptoms of congestive heart failure responded favorably to the conventional symptomatic measures employed for this purpose. In this patient these consisted of the use of digitalis, mercurial diuretics, oxygen, and a low-salt diet. Two episodes of bronchitis and pneumonia responded dramatically to adrenal steroid therapy in moderately large doses. Considerable improvement in the patient's cardiac condition had already occurred as a result of symptomatic measures so that no evaluation of the effect of steroids alone upon the heart disease could be made. However, by analogy with the favorable response of the pulmonary involvement, it seems logical to try adrenal steroid therapy in patients with myocardial involvement due to Toxocara infection if the usual symptomatic measures failed to result in improvement.

SUMMARY

A $2\frac{7}{12}$-year-old Negro girl with visceral larva migrans is described in whom severe myocardial involvement occurred followed by complete recovery. This is the first clinical report of myocardial involvement associated with this parasitic infection with recovery of which we are aware. The diagnosis and management of this new complication of visceral larva migrans are briefly discussed.

REFERENCES

1. Perlingiero, J. G., and Gyorgy, P.: Chronic Eosinophilia: Report of a Case With Necrosis of Liver, Pulmonary Infiltrations, Anemia and Ascaris Infestation, Am. J. Dis. Child. **73:** 34, 1947.
2. Zuelzer, W. W., and Apt, L.: Disseminated Visceral Lesions Associated With Extreme Eosinophilia. Pathological and Clinical Observations in a Syndrome in Young Children, Am. J. Dis. Child. **78:** 153, 1949.
3. Beaver, P. C., Snyder, C. H., Carrera, G. M., Dent, J. H., and Lafferty, J. W.: Chronic Eosinophilia Due to Visceral Larva Migrans, Report of Three Cases, Pediatrics **9:** 7, 1952.

4. Karpinski, F. E., Evert-Suarez, E. A., and Sawitz, W. G.: Larval Granulomatosis (Visceral Larva Migrans), A. M. A. J. Dis. Child. **92:** 34, 1956.
5. Smith, M. H. D., and Beaver, P. C.: Persistence and Distribution of Toxocara Larvae in the Tissues of Children and Mice, Pediatrics **12:** 491, 1953.
6. Brill, R., Churg, J., and Beaver, P. C.: Allergic Granulomatosis Associated With Visceral Larva Migrans. Case Report With Autopsy Findings of Toxocara Infestation in a Child, Am. J. Clin. Path. **23:** 1208, 1953.
7. Beautyman, W., and Wolf, A. L.: An Ascaris Larva in the Brain in Association With Acute Anterior Poliomyelitis, J. Path. & Bact. **63:** 634, 1951.
8. Dent, J. H., Nichols, R. L., Beaver, P. C., Carrera, G. M., and Staggers, R. T.: Visceral Larva Migrans With a Case Report, Am. J. Path. **32:** 777, 1956.
9. Wilder, H. C.: Nematode Endothalmitis, Tr. Am. Acad. Ophth. **55:** 99, 1950-51.

Sarcoma of the leg in a newborn infant

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MALIGNANT tumors noted at birth are extremely rare, although many malignancies of childhood are considered to stem from embryonal rests and are therefore termed congenital. Fahey and Bollinger[1] in 1953 reported a case of congenital fibrosarcoma of the foot and the results of a thorough review of the literature. At that time, there was a total of 35 cases of congenital sarcoma, 17 occurring on the extremities. They felt that early amputation was the treatment of choice. A search of the available literature since 1953 reveals only one other case in a newborn child. Jensen, Martin, and Longino[2] reported 6 cases of digital neurofibrosarcoma in infancy seen at the Boston Children's Medical Center up to 1957. One of these lesions was probably present at birth. They recommended wide local excision of the tumor. Because sarcoma in the newborn is such an extremely rare tumor, no single clinic has been able to accumulate a great deal of experience with the lesion. This makes it difficult to develop a recommended mode of treatment. Therefore, it is felt that a case report with discussion of treatment is justified.

CASE REPORT

J. F., a 6 pound 4 ounce white male infant, was born on April 16, 1957, and appeared to be normal except for a tumor mass of the right lower leg just below the knee. Family history revealed a maternal aunt known to have had cancer of the cervix, treated with radium, with apparent cure. Two siblings were living and well. The mother, 23 years of age, stated that her pregnancy was unremarkable except that she generally did not feel as well during this pregnancy as she had with two previous ones. Positive findings on physical examination of the infant were limited to the right lower extremity. On the anterolateral aspect of the right lower extremity, in the region of the head of the fibula and tibia, there was a 4 by 5 cm. hard, immobile mass with poorly demarcated edges. There was a central soft cystic area about 2 cm. in diameter with bluish discoloration (Fig. 1).

Complete blood count and urinalysis were within normal limits. X-rays of the right lower extremity revealed a large soft tissue mass without evidence of bone involvement. Several tiny flecks of calcic density were noted in the area of the mass. Chest x-ray was negative.

On April 18, 1957, wide local excision of the tumor was carried out without cutting into the mass for biopsy. A venous tourniquet was placed above the tumor until it was excised by en bloc dissection. The mass was pale yellow and appeared to stem from the region of the periosteum of the head of

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Fig. 1. View of tumor of right leg of newborn prior to operation (note central cystic area).

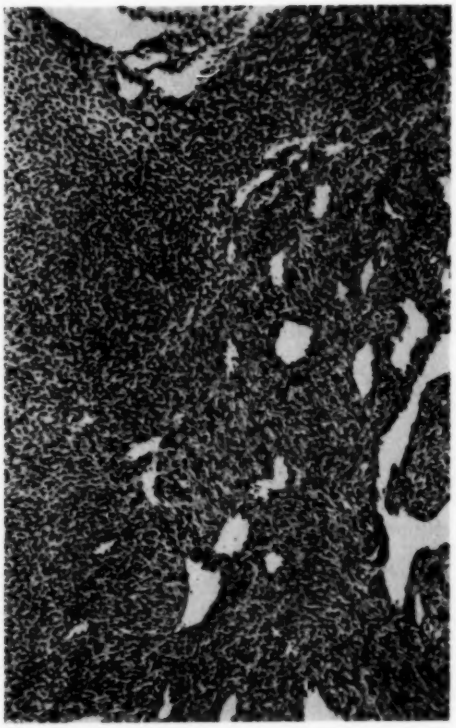

Fig. 2. Photomicrograph showing multiple sinusoidal spaces and groups of small cells. (×50; reduced ⅓.)

the fibula, where it was most adherent. This periosteum was stripped off with the tumor mass. Because of pseudopodium-like extensions, a great deal of the anterior muscle group was excised in an effort to avoid incision of any tumor tissue. The peroneal nerve was closely adherent, but was freed from the mass without sacrificing the nerve. A marked amount of edema in the tissue planes was encountered during the dissection.

Microscopic examination of the tumor revealed multiple dilated and irregular vascular spaces with a simple endothelial cell lining. In a few isolated areas these sinusoidal spaces were associated with rounded aggregates of small, poorly defined cells. The neoplasm extended into voluntary muscle and tendinous connective tissue. In most zones the vascular spaces were well defined, but in other areas the tumor was composed of large groups of spindle cells showing a few mitotic figures. Fat was entrapped or included in the neoplasm and in one zone there was metaplastic cartilage which appeared to be benign. The tumor extended to within a few millimeters of the epidermis superficially and to the periosteum. The local pathologist's diagnosis was malignant hemangiopericytoma. Slides were reviewed by Dr. Dorothy Andersen, in whose opinion it was a malignant embryonal tumor with rhabdomyosarcoma predominating. She advised regional node dissection in addition to the local excision. Therefore, on May 3, 1957, inguinofemoral node dissection was carried out on the right. Pathological study of these nodes proved negative.

It has been over 2 years since operation, with no sign of either local or distant metastasis. X-rays are normal. The child walks well, with no foot drop or obvious weakness. There is slight assymmetry of the right leg

Fig. 3. Section of tumor showing invasion of striated muscle and numerous spindle cells. (×80; reduced ⅓.)

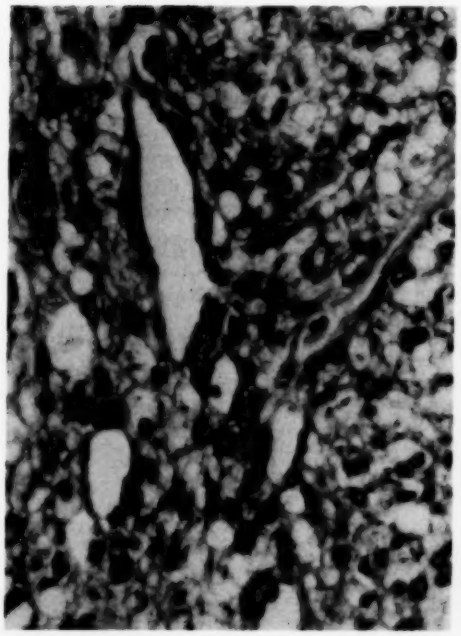

Fig. 4. High-power view showing entrapped fat and poorly defined cells. (×450; reduced ⅓.)

due to loss of muscle substance, as shown in Fig. 6.

DISCUSSION

The etiology of this tumor or of any sarcoma of the newborn remains obscure. Whatever the causative agent, it must be a potent one with a maximum duration of action of 9 months. Since viruses have been incriminated in some congenital defects, one might postulate a viral origin. Of the 17 cases reviewed by Fahey and Bollinger, only 7 cases, shown below in Table I, for one reason or another could be followed long enough for evaluation of treatment.

This author feels that it would be unwise to make any strong recommendation for mode of therapy on the basis of this small series. As Pack[3] and others[6, 7] have noted, certain neoplasms in infants and children, such as juvenile melanoma and certain liposarcomas, may present a highly malignant histological appearance but behave benignly from a clinical standpoint. It was mainly on the basis of this observation that it was decided not to amputate the extremity in the case reported here. One must not be too conservative, however, and simply enucleate such a tumor.[2] Pack and Ariel[3] feel that recurrence of a fibrosarcoma is probably due to pseudopodium-like strands of tumor extending out radially from the gross tumor. This morphology was observed in this case and every attempt was made to carry dissection beyond these extensions.

Table I

Number of cases	*Treatment*	*Results*
5	Amputation	4 living 2-10 years
1	Local excision	1 living 2-10 years
1	X-ray therapy	1 living 2-10 years

Fig. 5. Section showing proximity of tumor to the epidermis. (×20; reduced ⅓.)

Fig. 6. View of right leg 2 years after operation following local excision and regional lymph node dissection.

SUMMARY

1. A case of sarcoma of the leg in a newborn infant is presented.

2. The rarity of this type of case makes it difficult to set rigid criteria for modes of therapy. Treatment must be individualized after all known factors are weighed.

3. Wide local en bloc dissection with regional lymph node dissection appears to be a satisfactory mode of treatment for sarcoma of the newborn.

REFERENCES

1. Fahey, J. J., and Bollinger, J. A.: Congenital Sarcoma of the Foot, A. M. A. Am. J. Dis. Child. **86:** 23, 1953.
2. Jensen, A. R., Martin, L. W., and Longino, L. A.: Digital Neurofibrosarcoma in Infancy, J. Pediat. **51:** 566, 1957.
3. Pack, G. T., and Ariel, I. M.: Sarcomas of the Soft Somatic Tissues in Infants and Children, Surg. Gynec. & Obst. **98:** 675, 1954.
4. Andersen, Dorothy: Tumors of Infancy and Childhood, Cancer **4:** 890, 1951.
5. Wells, H. G.: Occurrence and Significance of Congenital Malignant Neoplasms, Arch. Path. **30:** 535, 1940.
6. Spitz, Sophie: Melanomas of Childhood, Am. J. Path. **24:** 591, 1948.
7. Craig, J. M.: Personal communication, 1956.

TROPICAL PEDIATRICS

Hemorrhagic fever in children in Thailand

Report of 69 cases

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DURING 1958 Thailand recognized its first epidemic of hemorrhagic fever which was important because of the high rates of morbidity and mortality. It was unique in that it was found only in children and only in the indigenous population. In these respects, as well as in the symptomatology, it differed from previously described hemorrhagic fevers in other Asian countries. Because sporadic cases of the disease had been seen for years in Thailand, but not recognized as hemorrhagic fever until the 1958 epidemic, it is believed by the author that the disease most likely occurs in other Asian countries in heretofore unrecognized forms. It is the purpose of this paper to point out certain features of the disease which may assist in its diagnosis in countries where it may be found in a similar endemic form.

This study is based upon a series of 69 cases diagnosed during the calendar year of 1958 at the 160 bed Bangkok Sanitarium and Hospital. Data have been gathered from the records of these patients and represent the volunteered complaints. Solicitation of specified definite data for a study was not done at the time; therefore in every case the symptoms were of a major nature. There was probably an equal number of cases, which because they lacked some of the criteria of the typical cases, could not be definitely diagnosed as hemorrhagic fever, and these were not included in the study.

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CLINICAL FEATURES

Clinical features in most cases were numerous, suggesting that many organs of the body were affected. An attempt has been made to classify this material according to systems (Fig. 1).

All children (100 per cent) had fever varying from 101° to 105° F. The fever was usually present several days before the onset of more critical symptoms and lasted throughout the 1 to 2 weeks' course of the illness. Respiratory symptoms of cough and pharyngitis were seen frequently (40 per cent); dyspnea and cyanosis were present in 10 to 15 per cent of the most critically ill and moribund patients who had bronchopneumonia and pleural effusion; x-ray evidence of pulmonary involvement was found

Fig. 1. Clinical features in 69 cases of hemorrhagic fever.

in the majority of cases (60 per cent). At some time in the course of the disease, most of the children had any or all of the following gastrointestinal symptoms: nausea and vomiting (70 per cent), anorexia (21 per cent), abdominal pain (25 per cent), and either diarrhea (13 per cent) or constipation (25 per cent). Hepatomegaly, with the liver enlarged 1 to 4 cm. was common (45 per cent) and often helped to confirm the diagnosis in an obscure form of the illness.

Bleeding tendencies were seen in all cases, most often in the form of purpura, a hemorrhagic petechial rash, or ecchymoses about the site of injections. Some patients with or without skin manifestations had hematemesis (22 per cent), melena (15 per cent), epistaxis (10 per cent), a positive tourniquet test, or occasionally a subarachnoid hemorrhage. In this study no case qualified as hemorrhagic fever unless some bleeding tendency was present.

A few children had a maculopapular rash, not petechial, while showing other hemorrhagic manifestations.

Symptoms relative to the central nervous system occurred often enough to confuse the diagnosis with possible meningitis. Headache, drowsiness, restlessness, twitching, and convulsions were seen in most critically ill children and in nearly all fatal cases.

A large proportion of the children were critically ill. The terminal cases almost invariably presented a peculiar shocklike state in which the extremities became clammy, cold, and cyanotic, while the body remained hot and feverish. Cyanosis, dyspnea, and convulsions were terminal manifestations. The sequence of symptoms and findings is depicted in several representative case studies which follow later in the paper.

In this series, there were 16 deaths (23 per cent). Fourteen of the 16 deaths, however, occurred in children hospitalized less than 48 hours. Most of these deaths were of patients brought to the hospital in a moribund state. Since many children recovered completely after being in an extremely critical condition, it was thought that therapy instituted early was probably lifesaving. Deaths were most common in infants under 1 year of age. Five of the 13 infants under 1 year of age with hemorrhagic fever died, giving a mortality rate of 38 per cent in this group as compared with a general mortality rate of 19 per cent for all age groups.

LABORATORY FINDINGS

Hemoconcentration (hemoglobin above 15 Gm.) was found in 19 per cent of the cases and was no doubt due to the frequent vomiting. Hemoglobin concentrations as high as 20 Gm. per cent were noted.

The majority (53 per cent) of cases had a normal white blood count (5,000 to 10,000). Leukocytosis was present in 38 per cent, an occasional case showing a leukocytosis of as much as 40,000. Only 9 per cent had a true leukopenia of less than 5,000.

The most characteristic laboratory finding was the platelet count, which was taken by the indirect method in 62 of the 69 cases. Of 7 cases in which no platelet count was performed, all had such bleeding tendencies as purpura, epistaxis, melena, or hematemesis. A thrombocytopenia of less than 100,000 per cubic millimeter was found in 65 per cent of 62 cases. Interestingly enough, 12 of these showed bleeding tendencies other than purpura. An additional 13 per cent of the patients had platelet counts between 100,000 and 150,000 at some time during their ill-

ness, and all of these had purpura. It was found that the number of platelets increased very rapidly with improvement of the patient; for example, within 2 days a count increased from 62,400 to 297,000; another increased from 62,000 to 698,400 in 1 day. Sharp rebounds in the platelet counts were also reported in Korean hemorrhagic fever by Powell.[1] In many cases a patient with hemorrhagic spots still present showed a normal platelet count when first examined by us.

Urinalysis revealed essentially negative findings, although an occasional case showed a trace to 1 plus albumin. Cerebral spinal fluid examinations of patients with central nervous system symptoms all showed less than 10 cells per cubic millimeter, and for the most part no more than 2 cells. There was no elevation of total protein. The glucose level was elevated in several patients, but these had had intravenous glucose therapy previously.

Chest x-rays were made in 56 of the cases, and there was radiologic evidence of bronchopeumonia, with or without pleural fluid in 60 per cent of them. In many of these children the clinical findings did not suggest pneumonia, but because pneumonia was found in a high proportion of our early cases, routine chest x-rays were nearly always ordered.

Typhoid agglutination tests were undertaken, but in no case was there a titer higher than 1:40, with either the O or H antigen.

DIAGNOSTIC CRITERIA

To be considered as having hemorrhagic fever, an affected child had to demonstrate fever and some bleeding tendency and/or thrombocytopenia together with one or more of the following: bronchopneumonia or other respiratory manifestations, hepatomegaly, or gastrointestinal symptoms.

CASE HISTORIES

Case 1 (31075). The patient, a 5-year-old Thai girl, entered the hospital on Oct. 9, 1958, having had a high fever and cough for 4 days, and nausea and vomiting for 3 days. Examination showed a thin, well-developed child who was very restless and critically ill. Significant findings were: temperature, 101° F.; respiration rate, 28 per minute, and pulse, 112 per minute. Several 1 to 2 cm. ecchymotic spots were seen on both buttocks at injection sites and a few 2 to 5 mm. purple macular spots were found on the arms and forehead. There was slight scleral injection. The throat was red with hypertrophic tonsils and the tongue was coated. Shotty, nontender cervical nodes were palpable. The heart showed a moderate tachycardia, but the rhythm was regular with no murmur. There were right basal dullness and râles bilaterally at both bases. Generalized abdominal tenderness was present. The liver was enlarged 2 cm. below the right costal margin. The spleen was not palpable.

Pertinent laboratory work showed hemoglobin, 18.5 Gm.; red blood count, 6.85 million per cubic millimeter; white blood count, 12,400 per cubic millimeter; neutrophils, 37 per cent; stab cells, 31 per cent; lymphocytes, 32 per cent and platelets, 13,000 per cubic millimeter. A typhoid agglutination test was O negative, H 1:40. No urine specimen was obtained. The chest x-ray showed right bronchopneumonia with pleural effusion.

The child complained of abdominal pain soon after admission to the hospital. By evening she was in a state of shock with cold clammy extremities. Her body was warm. She became more restless, pulseless, and cyanotic around the lips and hands. The following morning at 7:00 A.M. she was drowsy; the heartbeat was 160 per minute, respiration 60 per minute, blood pressure 70/60. The pupils were dilated bilaterally with sluggish reaction to light. At 9 A.M. she began having generalized convulsions. Breathing became more shallow, and in spite of therapy with chloramphenicol, penicillin, and streptomycin, intravenous fluids, and cortisone, she died. Intracardiac Adrenalin was administered without benefit.

Pertinent findings at autopsy showed bilateral pleural effusions of approximately

100 c.c. on each side. Externally there were petechial hemorrhages over the pleural surfaces. Microscopically, interstitial pneumonia was found in the lungs. The liver was enlarged 2 cm. below the right costal margin, and was pale pink in color. Staining for fat on microscopic sections showed diffuse fatty infiltration. The spleen was contracted, and the pulp was a deep red. Microscopically small granulomatous foci were noted in the centers of the Malpighian bodies, with an accompanying fibrinoid degeneration. Mesenteric lymph nodes were enlarged to 1.5 cm. in diameter, and had homogeneous cut surfaces. Microscopic examination showed reticular hyperplasia. All other organs showed no significant alterations. The brain was not examined.

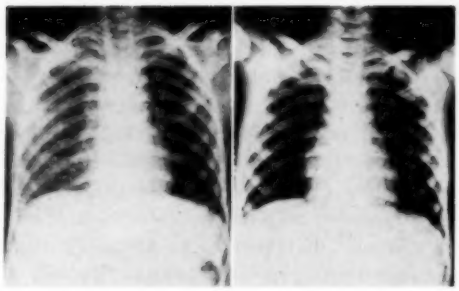
Case 2 (30914). The patient, a 2-year-old Chinese girl, was admitted on Sept. 27, 1958, with symptoms of fever and vomiting for 3 days, and generalized redness all over the body for 1 day. On examination, the temperature was 100° F. There was a faint macular eruption over the upper chest. The throat was injected. The heart and abdomen were normal and the lungs were clear. A tourniquet test was negative. The patient was started on penicillin, streptomycin, chloramphenicol, and intravenous fluids.

Pertinent laboratory findings were: hemoglobin, 11.5 Gm.; red blood count, 3.29 million per cubic millimeter; white blood count, 7,800 per cubic millimeter; and platelets, 16,450 per cubic millimeter. A typhoid agglutination test was H 1:20, O 1:40. A malarial smear was negative and a roentgenogram of the chest was within normal limits.

On September 28, the child was still febrile, but generally better. On September 30, the liver was palpable 3 fingerbreadths below the costal margin, and there was a pyrexia of 102° F. Cortisone was started.

On October 1, a platelet count was 50,630 per cubic millimeter, and 2 days later the child was improved and discharged.

Case 3 (29771). The patient, a 13-year-old Chinese boy, entered the hospital on July 14, 1958, complaining of fever for 10 days with chest and abdominal pain. He had had no bowel movement for 5 days and had been vomiting for 3 days.



A *B*

Fig. 2, *A*. Roentgenogram of the chest of Case 3, showing right bronchopneumonia. *B*. Roentgenogram of the chest of Case 3 6 days later, showing clearing.

Pertinent laboratory findings were homoglobin, 14 Gm. and white blood count, 5,000 per cubic millimeter. A typhoid agglutination test was H 1:20, O 1:20. The urine was negative.

Intravenous glucose in water infusions and chloramphenicol were started. On July 15, the patient was semiconscious with subnormal temperature and a cold and sweaty skin. He had convulsions lasting 3 minutes. The lungs were clear. A chest roentgenogram showed right bronchopneumonia with fluid in the right cardiophrenic angle (Fig. 2, *A*). During the day he passed blood rectally. Cortisone therapy was started.

On July 16, he was restless and had further convulsions. The sputum was bloody. A blood count showed hemoglobin, 10 Gm.; red blood cells, 3.25 million per cubic millimeter; white blood cells, 5,400 per cubic millimeter, and platelets, 39,000 per cubic millimeter.

By July 18 the patient had regained consciousness and complained of abdominal pain. He was restless and crying.

On July 20, the white blood count was 10,850 and the platelets 400,150 per cubic millimeter. The cerebrospinal fluid was clear, colorless and contained no cells; the glucose

was 69 mg. per cent and total protein, 16 mg. per cent. A repeat roentgenogram on this date showed complete clearing of the right lung (Fig. 2, *B*).

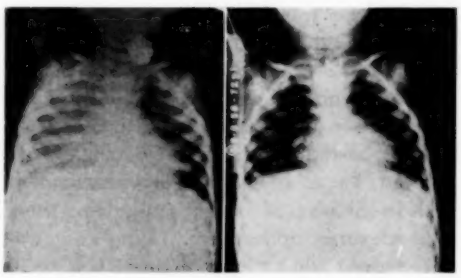
Case 4 (30016). A 3-year-old Thai boy was admitted on Aug. 1, 1958, because of recurrent fever for 15 days for which he had been given Chinese medicine. He had had a cough for 10 days and had developed spots on his body. He had been constipated for 2 days and ate poorly.

The temperature was 100° F. There were generalized ecchymoses and purpura. The eyelids were edematous, the throat injected, and the tongue coated. There was dullness over the right lung with râles. The abdomen was normal. The initial diagnosis was upper respiratory infection, pneumonia, and possible intoxication from the Chinese medicine.

Laboratory findings were hemoglobin, 12.5 Gm.; red blood count, 3.76 million per cubic millimeter; white blood count, 9,000 per cubic millimeter; and platelets, 37,600 per cubic millimeter.

The child was given daily injections of penicillin and streptomycin, as well as Terramycin and Metacorten. A clysis of dextrose in water was given.

On August 2, the chest roentgenogram showed right bronchopneumonia with pleural fluid (Fig. 3, *A*). The child was afebrile and alert. A bone marrow aspiration was done which showed hypocellularity with many basket cells present. There was an absolute decrease in the number of megakaryocytes, especially the platelet-producing ones.



A *B*

Fig. 3, *A*. Roentgenogram of the chest of Case 4, showing right bronchopneumonia with pleural fluid. *B*. Roentgenogram of the chest of Case 4, showing clearing.

Fig. 4. Age incidence of hemorrhagic fever.

On August 4, the right chest was aspirated and 30 c.c. of cloudy yellow fluid withdrawn and cultured but no bacterial growth developed. On August 6, the chest roentgenogram showed striking absorption of pleural fluid and resolving bronchopneumonia (Fig. 3, *B*), and by August 7, the patient was afebrile and was discharged.

INCIDENCE

Age. The highest incidence of the disease occurred in children less than 1 year of age. Thirteen of the 69 cases were found in this group. There was a gradual decline in incidence with increase in age (Fig. 4). Sixty one of the 69 cases occurred before the ninth year of age. This is highly suggestive that an increasing immunity develops in children as they may have had clinical or subclinical disease in their younger years.

Sex. The study was comprised of 40 males and 29 females. The preponderance of boys over girls parallels the consistently higher male population among our pediatric patients. A 6 months' pediatric admission census during 1958, for example, totaled 384 boys and 225 girls.

Ethnic group. A comparative study of the morbidity in this disease among our four predominant ethnic groups in the hospital was made. The average pediatric hospital occupancy is 57 per cent Chinese, 38 per

Fig. 5. Seasonal incidence of hemorrhagic fever.

cent Thai, 4 per cent American, and 1 per cent Indian. Not a single case of hemorrhagic fever was diagnosed among either the American or Indian children hospitalized during 1958; 23 per cent of the cases were among Thai children and 77 per cent among Chinese, which represents a correspondingly higher incidence among the Chinese than the Thai.

Season. The study was made for the entire year of 1958, divided into 24 periods of approximately 15 days each. The months of December, January, February, March, April, and May had no cases or only a single case, so for practical purposes it may be said that from December through May, hemorrhagic fever was almost nonexistent (Fig. 5). Beginning in June, there was a gradual increase in the number of cases with the peak occurring in September and the first 2 weeks in October, after which there was a precipitous decrease in the number of cases. The incidence of the disease, therefore, corresponds with the rainy season in Bangkok.

During the peak month of September there were 156 pediatric admissions to the hospital of which 20 or about 13 per cent of the children had hemorrhagic fever.

PATHOLOGIC OBSERVATIONS

Autopsies were performed in 5 of the cases. In these, the lungs, liver, and spleen consistently showed the same types of lesions. The pneumonia in the lungs was of an interstitial type. Negligible pulmonary edema was present and only scattered histiocytic cells were found in alveoli. Scattered small hemorrhages were found on the pleural surfaces in most instances. The livers were slightly enlarged, pale in color, and there were diffuse small collections of fatty material in the hepatic cells. Liver cell boundaries were poorly differentiated. Occasional foci of lymphocytes were noted, as well as occasional inflammatory cells between the liver cords.

The most specific lesion was found in the Malpighian corpuscles of the spleen. The size of the spleen varied from case to case; there was no more than a slight splenomegaly in any case. A granulomatous-appearing lesion was present in all stages of development in the central portion of the Malpighian bodies. Clumps of monocytoid cells with abundant lavender-colored cytoplasm were noted at an early stage. The cytoplasm resembled that of a "Russell body." In areas the cytoplasm of these cells appeared to fuse together in a syncytium. Scattered neutrophils were found also in these foci. The older, larger lesions almost had the appearance of tubercles with patchy fibrinoid between the inflammatory cells. This lesion may be similar to that mentioned as a "mononuclear cellular infiltration of the spleen" by Hullinghorst and Steer[2] in Korean hemorrhagic fever.

Mesenteric lymph nodes were enlarged in 3 cases, but showed only reticular hyperplasia. In 2 of these, small granulomatous foci, similar to those in the spleen, were noted in the follicles. Focal hemorrhages in the heart were found in 2 cases as well as patchy areas of myofibril degeneration. No accompanying leukocytic reaction was noted. One case had minimal adrenal hemorrhage in the medullary portion. A single case showed vacuolation and degeneration of cells in the islets of Langerhans, giving them a moth-eaten appearance. In no case was there any noteworthy pathologic finding in the kidneys. Examinations of the brain were not made.

Bone marrow examination showed a variable number of megakaryocytes; in some instances the number was increased and in

others decreased. Platelet-producing megakaryocytes, however, were uniformly few in number.

ETIOLOGY

Bacterial cultures of the pleural fluid were all negative. However, previous studies made in the Philippines in 1956 by Hammon,[3] of the University of Pittsburgh, on hemorrhagic fever, where the disease most nearly corresponds with it as manifested in Thailand, identified the etiological agent as a dengue type of virus, and the *Aedes aegypti* mosquito was named as the vector. Dr. Hammon, at the request of the King of Thailand, made a trip to this country during the epidemic and collected specimens upon which he is now carrying out virus studies.

TREATMENT

Most of the children, especially those with marked dehydration, received intravenous fluids in the form of glucose in water. Antibiotics such as Terramycin and a combination of penicillin and streptomycin and chloramphenicol were used but were of questionable value except perhaps in the prevention of secondary bacterial infections. Cortisone was used in most cases to combat the thrombocytopenia when the diagnosis was established, regardless of the severity of the disease. It was thought that the use of this drug was most beneficial. Dramatic results, in moribund cases apparently in terminal condition, were seen if the drug was started early enough. We believe this was largely the reason for the relatively low death rate (2 cases) in children hospitalized over 48 hours. Of the 14 who died after less than 24 hours' hospitalization, 12 died on the day of entry, before cortisone therapy was effective.

DISCUSSION

Prior to 1958, sporadic cases of hemorrhagic fever have occurred in Thailand, but have not been recognized as such. In our hospital we had seen this bizarre clinical pattern, with almost all of the patients dying rapidly in a shocklike state and responding poorly to supportive therapy. When we delved into the history of these children, we found all had been given Chinese medicine, usually for fever or some gastrointestinal upset. We had previously incriminated the Chinese medicine as the cause of death. In reviewing a number of these cases, it was noted that many were recorded as having a rash or coffee-ground type of emesis. Until this year's epidemic, purpura had not seemed to be the prominent presenting symptom.

Other diseases likely to be confused with hemorrhagic fever are primary thrombocytopenic purpura and bronchopneumonia, the latter especially when complicating measles. Typhoid fever may have many features in common with it, such as pyrexia, gastrointestinal complaints, splenomegaly, and a rash. A platelet count as well as typhoid agglutination tests are helpful in establishing the correct diagnosis.

Central nervous system symptoms often suggest meningitis, but examination of the cerebrospinal fluid easily differentiates the two. Our patients with hemorrhagic fever had no stiffness of the neck. Unfortunately, as stated above, the brains were not examined at autopsy.

Subclinical cases of hemorrhagic fever may masquerade as influenza, gastroenteritis, fever of unknown etiology, and in fact cannot usually be differentiated, although the diagnosis may be suspected.

The epidemiologic and pathologic findings in our Thailand cases differ somewhat from those reported from other oriental countries.[4] Hemorrhagic fever as seen in Korea affected adult Americans, and the kidney was the organ mainly involved.[5] Pneumonia was reported but the relative frequency of this complication was not given.[1] The hemorrhagic fever seen in the Philippines was similar but the severe pulmonary complication was not reported there and the mortality rate was not as high.[3]

SUMMARY

In Asia, where hemorrhagic fever can be (or is) endemic, it should be considered in

the differential diagnosis of cases of thrombocytopenic purpura, measles, bronchopneumonia, typhoid, influenza, "Chinese medicine poisoning," gastroenteritis, and fevers of unknown etiology. Sixty-nine cases of hemorrhagic fever in children seen at the Bangkok Sanitarium and Hospital during the 1958 Thailand epidemic are reported. Symptoms, physical and laboratory findings, age, sex, and seasonal incidences are discussed, and specific cases representing various manifestations are described.

I wish to thank the entire clinical staff of the Bangkok Sanitarium and Hospital for the use of their case histories, and especially Dr. Neil R. Thrasher, radiologist, for his interpretation of the x-rays.

Photographs of x-rays were taken by Dr. Khow Kar Yoke.

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REFERENCES

1. Powell, G. M.: Clinical Manifestations of Epidemic Hemorrhagic Fever, J. A. M. A. **151:** 1261, 1953.
2. Hullinghorst, R. L., and Steer, A.: Pathology of Epidemic Hemorrhagic Fever, Ann. Int. Med. **38:** 77, 1953.
3. Hammon, W. McD., et al.: Studies on Philippine Hemorrhagic Fever: Relationship to Dengue Virus. Presented at the Ninth Pacific Science Congress, Nov. 18-30, 1957, Bangkok, Thailand.
4. Barbero, G. J., Katz, S., Kraus, H., and Leedham, C. L.: Clinical and Laboratory Study of 31 Patients With Hemorrhagic Fever, A. M. A. Arch. Int. Med. **91:** 177, 1953.
5. Epidemic Hemorrhagic Fever (Editorial): J. A. M. A. **151:** 1410, 1953.

MEDICAL PROGRESS

Systemic lupus erythematosus

A review of certain recent developments in the study of this disease

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THREE detailed surveys of the disease systemic lupus erythematosus (SLE) have together covered the natural history, clinical symptoms, diagnosis, and many aspects of the treatment of the disease.[1, 2, 3] This article therefore deals only with certain developments in the study of the disease which have occurred recently and which have not been so extensively discussed.

ABNORMAL IMMUNOLOGICAL REACTIONS

Abnormal immunological reactions have been found more frequently and in greater number in SLE than in any other disease. In addition to their number, these reactions are notable in two respects. First, the abnormal antibodies which have been identified are capable of reacting with the patient's own tissues, and therefore the reactions appear to be autoimmune ones. Second, among these antibodies is a group which reacts with the constituents of the cell nucleus including nucleic acids; they probably represent the first clear example of antibodies to nuclear substances.

One of the most fascinating aspects of SLE is the LE cell. This cell results from the alternation of the nucleus of a leukocyte by a factor in the serum of the patient. The affected nucleus becomes swollen, is extruded from the cell, and is then engulfed by another leukocyte. This second leukocyte, containing within its cytoplasm the altered, extruded nucleus, is the LE cell (Fig. 1.). In recent years investigations employing immunological and histochemical techniques have led to an understanding of the mechanism of this phenomenon and concomitantly to demonstration of the existence of antinuclear antibodies.

The factor which causes LE cell formation can be absorbed from the serum by isolated cell nuclei or nuclear deoxyribonucleoprotein.[4, 5, 6] The latter consists of deoxyribonucleic acid (DNA) and the basic protein histone in salt linkage; it is the constituent of the nucleus with which the LE cell factor combines specifically. Both the DNA and the histone appear to be essential for the reaction.[7] After absorption of LE cell factor,

From The Rockefeller Institute, New York, N. Y.

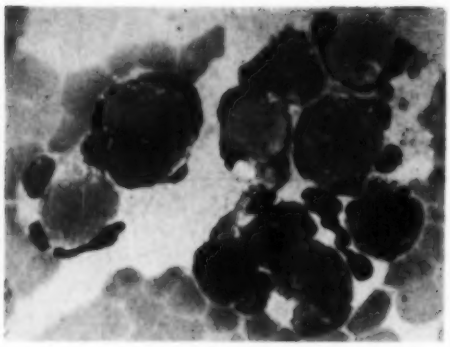

Fig. 1. A cluster of LE cells. Nuclei of phagocytizing cells are displaced to periphery by large inclusion bodies. Inclusion bodies consist of nuclei of other cells altered by combination with LE cell factor. At bottom right is altered nuclear material not yet phagocytized. After Wright's stain, inclusion bodies are various shades of pale blue.

whole nuclei or particles of nucleoprotein are coated with γ-globulin and are readily phagocytized by viable white blood cells with formation of inclusion bodies similar to those of typical LE cells.

The LE cell factor is not the only factor present in SLE serum which reacts with constituents of the nucleus. Other factors react with isolated DNA, purified histone, and a substance extractable from the nucleus in isotonic buffers which has not yet been characterized.[8, 9] These reactions can be demonstrated by standard immunological procedures such as hemagglutination,[10, 11] complement fixation,[12-15] precipitation,[16, 17] and passive cutaneous anaphylaxis.[18] It has been possible to separate many of the antinuclear factors from one another and to demonstrate that there is at least one separate factor which reacts with each of the above-mentioned nuclear constituents. An individual SLE serum may contain all, some, or none of the antinuclear factors. Fig. 2 demonstrates schematically the fractionation of the cell nucleus. Serum factors have been identified which react with each constituent shown except the nonhistone protein.

The serum factors have all migrated with the γ-globulins on electrophoresis and sedimented with the γ-globulins on ultracentrifugation. It has been possible to isolate in relatively pure form two of the serum factors: that which causes LE cell formation and that which precipitates with pure DNA. The former can be recovered from a complex with deoxyribonucleoprotein by digesting the complex with deoxyribonuclease (DNase), followed by elution from the residue at higher temperature or higher salt concentrations.[7] The latter can be recovered by digesting with DNase the equivalence point precipitates formed by SLE serum and DNA.[17] In both instances, the recovered factor reacts quantitatively with and is completely inactivated by antiserum to normal human γ-globulin; thus it possesses the immunological characteristics of typical human antibody globulin.

The serum titers of the antinuclear factors are highest during disease activity and diminish or disappear during spontaneous or therapeutic remissions.

The specificity which the antinuclear factors demonstrate toward constituents of the nucleus, the immunological nature of the methods which identify the factors, and the fact that the isolated factors have possessed the properties of typical human antibody γ-globulin, all suggest that the antinuclear factors are antibodies. The LE cell factor thus appears to be one member of a group of antinuclear antibodies.

The conclusion that the formation of LE cells is the result of an immunological reaction between a circulating antibody and a component of the cell nucleus is compatible

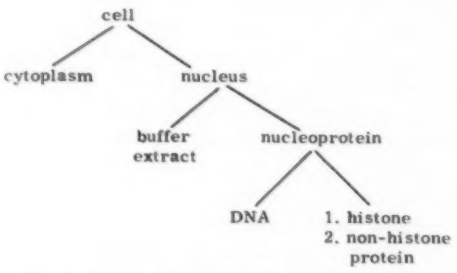

Fig. 2. Scheme of fractionation of the cell. Antibodies have been identified in sera from patients with SLE which react with each constituent shown except nonhistone protein.

with the recent histochemical investigations of the LE cell by Godman and Deutsch.[19] They have demonstrated that the initial alteration of the affected nucleus coincides with a sudden rise in the total protein of the nucleus, which would be expected if an antibody were entering the nucleus, rather than by an enzymatic depolymerization of the DNA as was originally thought.

In addition to the antinuclear antibodies, at least one and perhaps more serum factors occur which fix complement with constituents of cell cytoplasm.[15, 20, 21] One such factor reacts with a constituent of microsomes which is not RNA. Although resembling the Wassermann reagin, the anticytoplasmic factors have not proved identical with it. The anticytoplasmic factors also migrate with γ-globulin on electrophoresis and sediment with it on ultracentrifugation. They have not yet been isolated, however, and therefore have not yet been shown to exhibit many of the properties of typical antibodies.

Although the antinuclear and anticytoplasmic factors appear characteristically in SLE, they also occur in other diseases. Positive LE cell preparations have been reported frequently in patients with clinical rheumatoid arthritis and occasionally in a number of other diseases.[1, 22] γ-globulins which react with cell nuclei have been identified in scleroderma and dermatomyositis.[23, 24] In our experience, complement fixation reactions with nuclear constituents not containing nucleic acids have appeared occasionally in patients with Sjögran's syndrome, biliary cirrhosis and cirrhosis of unexplained origin. However, reactions with nuclear constituents containing nucleic acids have been identified thus far only in patients with SLE. Anticytoplasmic factors have had a wider distribution than antinuclear factors, appearing in SLE, scleroderma, Sjögran's syndrome, various types of cirrhosis, macroglobulinemia, and occasional cases of leukemia.

The antinuclear and anticytoplasmic antibodies add to the list of unusual antibodies known to occur in SLE. Antibodies to red blood cells have been demonstrated by the Coombs method.[1] Antibodies to white blood cells and platelets have been demonstrated by agglutination techniques.[25, 26] The false positive Wassermann reaction is evidence for the existence of the Wassermann reagin or antibody.[1] In addition, a circulating γ-globulin has been demonstrated to prolong the clotting time probably by interfering with thromboplastin,[27] and the characteristic renal lesion has been shown to be the site of extensive deposition of γ-globulin.[28, 29, 30] Most of the latter antibodies which react with a specific cell or protein appear to differ from the antinuclear and anticytoplasmic antibodies which demonstrate no species or organ specificity and which can, therefore, react with constituents of most cells.

Certain of the unusual antibodies can be detected readily in a clinical laboratory and therefore have proved of diagnostic value. A positive Coombs test, a positive Wassermann reaction, a prolonged clotting time, and a positive LE cell preparation comprise a tetrad which is diagnostic of SLE. The presence of any one of these abnormalities suggests the diagnosis.

The mechanism which gives rise to the unusual antibodies is unknown. The large number of antibodies which appear suggests that there is an abnormally reactive system for antibody synthesis which produces antibodies to normal cell constituents. The possibility that the cell constituents themselves are altered and made antigenic has not been excluded, however.

The pathogenic significance of the various unusual antibodies is also not clearly understood. It appears that under certain circumstances antibodies to red blood cells and perhaps to platelets can give rise to the hemolytic anemia or thrombocytopenic purpura which sometimes occurs in the disease, but it is uncertain whether or not other of the unusual antibodies have a pathogenic role. In particular, the antinuclear antibodies appear incapable of crossing the membrane of a viable cell and thus affecting adversely a cell functioning normally in the body. It is possible, however, that these antibodies, which are capable of reacting with

the nucleus of any cell in the body, may react with nuclei of abnormal cells or cells which are in the process of distintegration. The hematoxylin bodies, which probably are combinations of nuclear material and γ-globulin, may have such an origin. In this latter way, antinuclear antibodies may contribute to the appearance of tissue lesions. At the present moment, however, the pathogenic significance of the various unusual antibodies remains unsettled. It is entirely possible that they are by-products of an altered immunological response rather than decisive pathogenic agents themselves.

The various abnormal antibodies represent immunological reactions of an immediate type. Some evidence also suggests the existence of an unusual delayed type of sensitivity.[31] When injected intradermally with homogenates of their own leukocytes, many patients with SLE have developed erythema and induration at the injection site with an inflammatory infiltration. This reaction usually appears between 10 and 18 hours after injection and lasts for 24 to 48 hours. Occasionally reactions occur later. The reactions have been independent of the presence of abnormal circulating antibodies and have occurred in both the active and quiescent stages of the disease. Of 31 patients with SLE tested, 18 had distinct and 7 had equivocal skin reactions. Positive reactions have also been found in 2 of 5 patients with rheumatoid arthritis, 1 of 6 patients with rheumatic fever, and 2 of 4 patients with coronary occlusions. Six normal persons and 10 persons with various other diseases have had negative reactions.

This skin reaction has not yet been shown to be a reaction of delayed hypersensitivity, though there are many points of similarity between the two. It is possible that it represents an unusual type of skin response initiated by certain types of tissue injury in the patient.

Whatever the pathogenic significance of the unusual antibodies or the peculiar skin reaction may prove to be, the demonstration of their existence by a variety of standard immunological methods indicates the presence of a grossly abnormal immune system. Characterization of the nature of this unusual immune system may provide a significant clue to an understanding of the pathogenesis of SLE. Furthermore, the profusion of autoimmune reactions makes this disease an excellent subject for study of the nature of autoimmunity and its role in human disease.

INCIDENCE OF THE DISEASE

Ten years ago SLE was considered a rare and usually fatal disease. It was recognized almost exclusively in its late stages. In recent years, particularly since introduction of the LE cell phenomenon as a diagnostic aid, the diagnosis has been made more frequently, and less severe stages of the disease with varying manifestations have been recognized. The border lines distinguishing this disease from others have become less distinct. As a consequence, no unequivocal information is available dealing with the incidence of SLE in the general population. Dubois,[32] using classical clinical and pathological manifestations and positive LE cell preparations as criteria, has presented evidence obtained from the case records of the Los Angeles General Hospital suggesting that SLE is approximately as common as acute leukemia and about half as frequent as acute rheumatic fever. Similar data from other hospitals are not available for comparison.

Whether or not the incidence of the disease is increasing remains unsettled. Many have felt that the increasing number of recognized cases is solely a result of earlier and more frequent diagnosis. The possible correlation between drug sensitivity and the onset of SLE, which led to the suggestion that hypersensitivity to chemicals was causing an increased incidence of the disease, has not been proved. However, one interesting study suggesting an absolute increase in incidence of the disease has appeared from a small, stable community in Sweden.[33] Virtually all members of this community are served by one hospital, and analysis of the hospital records suggests a striking rise in

the number of cases of SLE in the past decade. A less satisfactory analysis of hospital records in a large midwestern hospital in the United States does not show such an increase.[34]

Evidence for a familial occurrence of SLE is emerging. A number of instances have been reported in which two members of the same family have developed SLE, usually mother and child or siblings.[35] At least 2 instances of SLE in identical twins have occurred.[36, 37] A most interesting report is that of Leonhardt.[38] He presents data on a family of 14 children. Four had SLE with hypergammaglobulinemia and 3 of these have died. Three other children are asymptomatic but have hypergammaglobulinemia. The mother and father are apparently well, but no other relatives have thus far been reported upon.

The mechanism whereby mother and offspring would develop SLE is unknown. It is known that the LE cell factor and presumably other unusual antibodies cross the placenta, enter the circulation of the fetus and can be identified in the serum of the newborn.[39] The LE cell factor disappears from the serum of the newborn after a few weeks, which is the usual disappearance time for maternal γ-globulin, and no report of harm to such newborn infants has yet been made. Data on the familial incidence of the disease is so fragmentary, however, that it is impossible to say whether any serum factors were transferred from mother to child in the cases in which the disease subsequently occurred in the child. Very often the disease appears in the offspring many years after birth, long after any factors received via placental transfer would have disappeared from the blood.

Evidence for a hereditary predisposition to the disease has also arisen from study of relatives of patients with SLE. Preliminary examination of the sera of immediate relatives of 18 patients with classical SLE has led to the identification of hypergammaglobulinemia, positive rheumatoid serological reactions, or positive complement fixation reactions with tissue extracts in at least one person in ten of the eighteen families.[40] In one instance, 4 of 7 members of a family thus far studied were abnormal. In another instance, mother and daughter had SLE and a granddaughter, aged 14, has on one occasion had a positive LE cell preparation. In general, the relatives showing serological abnormalities have been asymptomatic. Some years ago Moore and Lutz[41] demonstrated that a positive Wassermann reaction can antedate the appearance of SLE by many years, and also that asymptomatic persons with false positive Wassermann reactions are more likely to develop rheumatoid arthritis or SLE than any other disease. Taken together, these data indicate that there is a predilection for an abnormal immunological response in certain families, which may express itself as rheumatoid arthritis or as SLE, or may simply manifest itself as a serological abnormality without evidence of clinical disease.

RENAL DISEASE

Renal disease provides the most difficult clinical problem in SLE today. This appears to be due to a change in the natural history of the disease under the influence of steroid therapy. Most systemic manifestations of SLE will respond to steroids at least temporarily. Acute fulminating fatal crises of SLE have almost ceased to occur. Subacute bacterial endocarditis is rare compared to its incidence 20 years ago. As a consequence the average length of life of the patient is increasing and renal disease has come to the fore as the major problem in management and as the prime cause of death.

In the typical renal disease of SLE, the basement membrane of the glomerulus is thickened and there is deposition of fibrinoid material, giving an appearance of rigidity to the glomerular capillaries. This has been termed the "wire-loop" lesion. In addition, there may be focal necrosis of the capillary tuft and hyaline thrombi in capillaries. Hematoxylin bodies are frequently observed in the capillaries. These lesions are focal in nature, though they may extend throughout the kidneys.

The origin of the renal lesion has remained obscure. In view of the presence of many different types of antibodies in the sera of patients with SLE it has been suggested that antibodies to the kidney are responsible for the renal lesion. No specific anti-kidney antibodies have ever been recovered, however. Both the anticytoplasmic and antinuclear antibodies are capable of reacting with kidney cells, but this reaction is not specific for the kidney and occurs with most other tissues in the body.

The possibility that immune mechanisms are involved has received support from studies conducted with fluorescent antibody techniques.[28-30] These studies have shown deposition of γ-globulin between the epithelial and endothelial membranes of the glomerulus and in the area of hyaline thrombi as well. This deposition of γ-globulin also occurs in glomerulonephritis, amyloidosis, and polyarteritis nodosa. The mechanism of deposition is not known, though it apparently is not caused by exudation at an inflamed area. Whether this γ-globulin is directly involved in initiation of the renal lesions or is merely a by-product of the responsible process is also unknown. The γ-globulin from the renal lesion has not yet been isolated or characterized and an experimental model of the renal disease does not yet exist.

Treatment of SLE renal disease has proved difficult and the results obtained have been contradictory. Doses of corticosteroids which appeared to influence other manifestations of the disease have usually been found to leave the renal abnormalities untouched. Muehrcke and his associates[42] examined serial renal biopsies from many patients who were receiving corticosteroid therapy. Their findings suggested that this therapy did not alter the morphological appearance of the renal lesion; rather, the lesions progressed almost unabated. Consequently, it has been felt by many that steroids are of little or no value.[43-45]

This view can be questioned, however, for successful treatment has been reported.[1, 32] In many instances of therapeutic failure just enough steroid treatment has been employed, in terms of both size of dose and duration of administration, to provide symptomatic improvement. Such a regimen is usually inadequate to induce remission in the renal lesion. Much more intensive and longer courses appear to yield considerable success.[32, 46] In some instances of successful therapy, steroids could be discontinued after the remission was obtained; in other instances low doses were required continuously.

In the past 3 years 75 per cent of the patients with SLE seen at the Hospital of the Rockefeller Institute have had varying degrees of renal disease. All patients were hospitalized and treated with corticosteroids, usually prednisone, until azotemia and hematuria had disappeared and proteinuria had cleared or stabilized. This required from 2 months to 6 or 7 months of therapy, depending upon severity of the lesion. The doses of prednisone employed were approximately 40 to 50 mg. per day in an average adult. With treatment for this period of time, a high percentage of patients have shown improvement in renal status. Only two of 27 patients with renal disease on admission have died with renal failure within 3½ years; one of these patients was not treated as described above, and the other entered the hospital with evidence of advanced chronic glomerulonephritis, including a blood urea nitrogen of 200 mg. per cent. Two others currently have persistent hematuria, though less than at the beginning of therapy. The remainder have had either complete return of renal function to normal, including urea clearance, or have proteinuria of less than 0.5 Gm. per day or slight impairment of urea clearance as the sole residue of the renal disease.

An example of improvement of severe renal disease was observed in a woman of 32 years of age who had 70 pounds of edema fluid, hypertension, a blood urea nitrogen of 100 mg. per cent, marked hematuria, and a urinary protein loss exceeding 18 Gm. daily. She was treated with 40 to 50 mg. of prednisone daily for 6 months. At

the end of that time the hematuria, azotemia, and edema had disappeared. She returned home with hypertension and proteinuria of 7 Gm. per day. During the ensuing year, corticosteroids were gradually withdrawn and now her proteinuria is 3 Gm. per day, the hypertension has disappeared, and she is asymptomatic and leading a normal life. Particularly impressive are the experiences with younger people who have hematuria and proteinuria up to 6 Gm. per day without azotemia. Fourteen such patients, who were maintained on treatment for from 2 to 5 months, have shown complete return of renal function to normal. Pollack and associates[47] have recently found morphological evidence of improvement of renal disease when large doses of steroids are given for long periods of time.

The mechanism of improvement under corticosteroid therapy is unknown. Corticosteroids appear to inhibit antibody synthesis; however, improvement of the renal lesion would presumably require resorption of γ-globulin already deposited in glomeruli. No one has studied serial renal biopsies with the fluorescent antibody technique during development and disappearance of the lesions to determine what changes occur in the γ-globulin deposits.

Not all cases of renal disease can be expected to respond to therapy. Lesions resembling acute nephritis or nephrosis appear responsive, whereas those resembling chronic nephritis appear refractory. Some patients who do respond will undoubtedly have relapses. However, experiences to date in the treatment of SLE renal disease certainly do not permit the view that the kidney lesion cannot be reversed with treatment. Furthermore, the successes thus far obtained argue strongly in favor of treating all patients early and thoroughly in the hope of avoiding the development of severe renal disease, and thus greatly prolonging the life span of the patient.

GENERAL THERAPY

No major new developments in therapy of the disease have occurred. More experience has been gained in the use of antimalarial drugs, however, and, as in the case of renal disease, some refinements of current methods appear possible.

Antimalarial drugs are highly effective in discoid lupus erythematosus.[48] They have been used alone and in conjunction with corticosteroids in SLE. In neither of the latter instances are there adequate control studies to prove or disprove efficacy of the antimalarial agents. Dubois[32] has presented considerable evidence suggesting benefit from antimalarial drugs alone in SLE. Both he and others often employ them with steroids. One of the most widespread impressions is that antimalarial agents permit earlier and more rapid discontinuance of steroid therapy; this has not been established. The doses used vary from 100 to 300 mg. of atabrine per day or its equivalent in other drugs. Chloroquin and Plaquenil have been widely used because of the yellow discoloration of the skin from atabrine.

The mechanism of action of antimalarial drugs is entirely unknown. It is known, however, that they combine readily with nucleic acids and deoxyribonucleoprotein.[49] This latter property allows them to inhibit completely the reaction of antinuclear antibodies with these substances if the nucleic acids have reacted with an antimalarial drug beforehand.[7, 9] In view of the fact that symptoms of SLE, especially the skin rash, are precipitated in some people by sunlight, that nucleic acids particularly absorb ultraviolet rays, and that antimalarial drugs combine with nucleic acids, it might be speculated that the usefulness of the drugs is due to a protective effect against actinic rays. There is no evidence to support this suggestion, however.

One of the most important problems in therapy today is the evaluation of the length of time corticosteroids should be continued and the dose which should be employed. Three distinct phases of response of the patient to therapy can be identified in most cases.[46] The first consists of improvement in clinical symptoms. The second includes improvement in the blood abnormalities, espe-

cially in the sedimentation rate, γ-globulin, albumin, and hemoglobin. The third consists of improvement of hematuria, azotemia, proteinuria, and the compromised urea clearance. When prednisone approximating 50 mg. per day in an adult is used, arthritis, fever, pleuritic pain, and rash usually improve or disappear dramatically within a few days. The blood picture does not improve that quickly. Blood abnormalities will begin to return toward normal only after treatment for 2 weeks to 1 month or longer. If renal disease is present, the hematuria is likely to persist for a minimum of 2 months after treatment has started. Thus, if treatment is discontinued or reduced after alleviation of symptoms alone, distinct abnormalities in the blood and kidney are likely to remain. The disease can then smolder, give rise to periods of exacerbation, and perhaps lead to more severe renal lesions. If, on the other hand, the treatment with steroids is continued until the blood and kidneys are normal, or the abnormalities have become stabilized, there is likely to be a much lower incidence of exacerbations and advancing renal disease, and a greater number of remissions permitting withdrawal of steroids.

While much more experience is necessary to establish the validity of the latter conclusions, the results of the use of this approach at the Hospital of the Rockefeller Institute are encouraging. In general, the average adult patient has been given the equivalent of 60 mg. of prednisone per day until clinical symptoms disappear; the dose has then been reduced to 40 mg. a day until the blood abnormalities and hematuria have disappeared and proteinuria is diminishing. The patients have then been put on gradually increasing activity until they resumed normal activity without the deterioration of the blood or renal status. The steroids have then been slowly withdrawn and the patients often maintained on antimalarial drugs. Of 38 patients treated in this manner in the past 3½ years, 31 have returned to normal activity. Fifteen of these are asymptomatic, and corticosteroids have been discontinued; 16 are asymptomatic on small doses of corticosteroids, usually with minor blood changes but no other abnormalities. Two are still symptomatic or have significant blood or renal abnormalities. Five have died, but only 2 of these deaths are directly attributable to the activity of the disease.

Ten of the patients have suffered relapses in the period of 3½ years. Two of these patients are in the group currently not receiving steroids, and 8 are in the group currently asymptomatic on small doses of steroids. The relapses have generally been more mild than the initial episodes of the disease. They have been discovered early either by reappearance of symptoms or of blood abnormalities, and all have responded to reinstitution of steroid therapy.

Occasionally, some blood abnormality has remained despite a return of the patient to normal in all other respects. An elevated γ-globulin level or an elevated sedimentation rate is the most frequent. Many of the patients now asymptomatic on low doses of steroids have an abnormality of one of these types.

"LUPOID" HEPATITIS

This term has recently been introduced, perhaps unwisely, to describe the liver disease which appears in a group of patients, who also have certain symptoms compatible with SLE and positive LE cell preparations.[50-53] The majority of these patients have been young women with enlargement of the liver, splenomegaly, and frequent spider angiomas. The pathological findings in the liver have been those of hepatitis or cirrhosis. Some of the patients have had histories compatible with antecedent episodes of viral hepatitis, but the majority give no clear evidence of an infectious origin of the liver disease. Hypergammaglobulinemia has often been extreme.

The majority of the patients have presented only a minimum of symptoms suggestive of SLE, for example, rash or arthralgia, and in most patients these symptoms have appeared after the hepatic lesion was apparent. In the cases reported by Bartholomew,[53] however, considerable clinical evidence sup-

porting a diagnosis of SLE was obtained, and the diagnosis could usually be made before the appearance of significant hepatic abnormality. In many of the cases, LE cell preparations have been positive, though often only weakly so. In others they have been negative. Satisfactory studies to identify a group of antinuclear antibodies have not been conducted but serum factors which fixed complement with cytoplasmic constituents have been identified in some cases.

The nature of the hepatic lesion, in particular in its early stages and in its relation to SLE, remains obscure. It appears to be established that: (1) an unexplained cirrhosis (or chronic hepatitis) occurs in young people, especially women, and (2) positive LE cell preparations and symptoms suggestive of SLE are present in some of these patients. Many patients with this type of cirrhosis present no evidence suggesting SLE, however. Furthermore, with the possible exception of some of the cases reported by Bartholomew, there are no reports of patients with SLE, established by current clinical and laboratory criteria, who have developed hepatic lesions of the type described. The presence of the LE cell phenomenon, particularly a weak one, is not diagnostic of SLE, for this occurs occasionally in a variety of diseases apparently unrelated to SLE.

SLE is a disease with many immunological abnormalities, of which the LE cell factor is one. Some of these abnormalities are present in other diseases, particularly those of a rheumatic type. On the other hand, immunological abnormalities have long been suspected in certain forms of liver disease, but supporting evidence has been meager. Thus, while it is conceivable that these cases of hepatic disease are an unusual form of SLE, it is also conceivable that some of their symptoms and serological abnormalities are a consequence of an immunological abnormality induced in some way by the mechanism responsible for the liver injury. Therefore it is probably wise to regard these cases of unexplained liver disease as fertile subject matter for study of abnormal immunological reaction in human disease, and hold in abeyance a decision as to their relationship to SLE as it is currently defined. In pursuit of this lead, it will be highly desirable to examine cases of SLE for evidence of liver disease, and to search for immunological abnormalities in cases of hepatic disease.

SUMMARY

Recent studies have identified many abnormal immunological reactions in SLE. Numerous different constituents of autologous cells act as antigens in these reactions, indicating the existence of an autoimmunity. The reactions involving components of the cell nucleus, of which formation of the LE cell is an example, represent the first known instance of the antigenicity of nucleic acids in human disease.

The pathogenic significance of the abnormal reactions, and the nature of the immunological response which gives rise to them, are unknown. However, classical forms of immediate and delayed hypersensitivity appear inadequate to explain the abnormalities. Thus a currently unappreciated type of immunological response may ultimately be shown to play a major role in SLE.

Certain of the abnormal reactions can readily be identified in the clinical laboratory and provide useful aids in diagnosis. Early and varied forms of the disease are being recognized.

Pending discovery of a decisive therapeutic regimen, corticosteroids and perhaps antimalarial drugs remain the major agents of treatment. With these materials considerable success can be achieved, even with many severely ill patients. There is an indefinite prolongation of life for most patients and the majority appear to be able to return to normal activity.

REFERENCES

1. Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H.: Systemic Lupus Erythematosus: Review of the Literature and Clinical Analysis of 138 Cases, Baltimore, 1955, Williams and Wilkins Company. Reprinted from Medicine, Vol. 33, No. 4, 1954.

2. Talbott, J., and Ferrandis, R.: Collagen Diseases, New York, 1956, Grune & Stratton.
3. Symposium on Systemic Lupus Erythematosus, J. Mt. Sinai Hosp. **24:** 233, 1959.
4. Miescher, P., and Fauconnet, M.: l'Absorption du facteur L. E. par des noyaux cellulaires, Experientia **10:** 252, 1954.
5. Holman, H. R., and Kunkel, H. G.: Affinity Between the Lupus Erythematosus Serum Factor and Cell Nuclei and Nucleoprotein, Science **126:** 162, 1957.
6. Friou, G.: Identification of the Nuclear Component of the Interaction of Lupus Erythematosus Globulins and Nuclei, J. Immunol. **80:** 476, 1958.
7. Holman, H. R., and Deicher, H.: The Reaction of the LE Cell Factor With Deoxyribonucleoprotein of the Cell Nucleus, J. Clin. Invest. **38:** 2059, 1959.
8. Holman, H. R., Deicher, H., and Kunkel, H. G.: The LE Cell and the LE Serum Factor, Bull. New York Acad. Med. **35:** 409, 1959.
9. Holman, H. R., and Deicher, H.: Multiple Antinuclear Antibodies in Systemic Lupus Erythematosus. (In preparation.)
10. Miescher, P., and Strassle, R.: New Serological Methods for the Detection of the LE Factor, Vox Sang. **2:** 283, 1957.
11. Goodman, H. C., and Bowser, R.: Use of Tannic Acid Hemagglutination Test in Detection of LE Factor, Fed. Proc. **17:** 56, 1958.
12. Ceppellini, R., Polli, E., and Celada, F.: A DNA-Reacting Factor in Serum of a Patient With Lupus Erythematosus Diffusus, Proc. Soc. Exper. Biol. & Med. **96:** 572, 1957.
13. Robbins, W. C., Holman, H. R., Deicher, H., and Kunkel, H. G.: Complement Fixation With Cell Nuclei and DNA in Lupus Erythematosus, Proc. Soc. Exper. Biol. & Med. **96:** 575, 1957.
14. Pearson, C., Craddock, G., and Simmons, N.: Complement Fixation Reactions With DNA and Leucocyte Material in Systemic Lupus Erythematosus, J. Lab. & Clin. Med. **52:** 580, 1958.
15. Asherson, G. L.: Antibodies Against Nuclear and Cytoplasmic Cell Constituents in Systemic Lupus Erythematosus and Other Diseases, Brit. J. Exper. Path. **40:** 209, 1959.
16. Seligmann, M.: études immunologiques sur le lupus erythémateux disseminé, Rev. franc. études clin. et biol. **3:** 558, 1958.
17. Deicher, H., Holman, H., and Kunkel, H. G.: The Precipitin Reaction Between DNA and a Serum Factor in Systemic Lupus Erythematosus, J. Exper. Med. **109:** 97, 1959.
18. Deicher, H., Holman, H. R., Kunkel, H. G., and Ovary, Z.: Passive Cutaneous Anaphylaxis Reactions With a Systemic Lupus Erythematosus Serum Factor and Isolated DNA, J. Immunol. (In press.)
19. Godman, G. C., and Deutsch, A.: A Cytochemical Study of the LE Bodies of Systemic Lupus Erythematosus, J. Exper. Med. **106:** 575, 1957.
20. Gajdusek, D. C.: An "Auto-immune" Reaction Against Human Tissue Antigens in Certain Acute and Chronic Diseases, Arch. Int. Med. **101:** 9, 1958.
21. Deicher, H., Holman, H. R., and Kunkel, H. G.: Anti-cytoplasmic Factors in the Sera of Patients With Systemic Lupus Erythematosus and Certain Other Diseases, Arthritis and Rheumatism. (In preparation.)
22. Sigler, J. W., Monto, R. W., Ensign, D. L., Wilson, G. M., Rebuck, J., and Lovett, J.: The Incidence of the L. E. Cell Phenomenon in Patients With Rheumatoid Arthritis, Arthritis and Rheumatism **1:** 115, 1958.
23. Friou, G. J., Finch, S. C., and Detre, K. D.: Interaction of Nuclei and Globulin From Lupus Erythematosus Serum Demonstrated With Fluorescent Antibody, J. Immunol. **80:** 324, 1958.
24. Bardawil, W. A., Toy, B. L., Galins, N., and Bayles, T. B.: Disseminated Lupus Erythematosus, Scleroderma, and Dermatomyositis as Manifestations of Sensitization to DNA-Protein. I. An Immunohistochemical Approach, Am. J. Path. **34:** 607, 1958.
25. Weinreich, J.: Thrombocytopenias and Platelet Antibodies, Vox Sang. **2:** 294, 1957.
26. Van Loghem, J. J., van der Hart, M., and Borstel, H.: The Occurrence of Complete and Incomplete White Cell Antibodies, Vox Sang. **2:** 257, 1957.
27. Lee, S. L., and Sanders, M.: A Disorder of Blood Coagulation in Systemic Lupus Erythematosus, J. Clin. Invest. **34:** 1814, 1955.
28. Mellors, R. C., Ortega, L. G., and Holman, H. R.: Role of Gamma Globulins in Pathogenesis of Renal Lesions in Systemic Lupus Erythematosus and Chronic Membranous Glomerulonephritis, With an Observation on the Lupus Erythematosus Cell Reaction, J. Exper. Med. **106:** 191, 1957.
29. Vazquez, J. J., and Dixon, F. J.: Immunohistochemical Study of Lesions in Rheumatic Fever, Systemic Lupus Erythematosus, and Rheumatoid Arthritis, Lab. Invest. **6:** 205, 1957.
30. Taft, L., Dineen, J., and Mackay, I.: Localization and Binding of Serum Proteins in Glomeruli and Kidney Biopsies in DLE and Glomerulitis, Australasian Ann. Med. **7:** 5, 1958.
31. Holman, H., and Deicher, H.: An Unusual Skin Reaction to Autologous Cell Constituents in Systemic Lupus Erythematosus. (In preparation.)
32. Dubois, E. L.: Systemic Lupus Erythematosus: Recent Advances in Its Diagnosis and Treatment, Ann. Int. Med. **45:** 163, 1956.
33. Svanborg, A., and Sovell, L.: Incidence of Disseminated Lupus Erythematosus, J. A. M. A. **165:** 1126, 1957.
34. Cannon, E., and Curtis, A.: A Survey of Lupus Erythematosus in the University of Michigan Hospital Since 1948, A. M. A. Arch. Dermat. **78:** 196, 1958.
35. McKusick, V. A.: Genetic Factors in Diseases of Connective Tissue, Am. J. Med. **24:** 283, 1959.
36. Davis, M. W., and Gutridge, F. H.: Dissemi-

nated Lupus Erythematosus in Identical Twin Sisters Associated With Diabetes Mellitus in One Case, J. Missouri M. A. **48:** 446, 1951.
37. Wagenhals, C. O., and Burgeson, P. A.: Systemic Lupus Erythematosus in Identical Twins, New York, J. Med. **58:** 98, 1958.
38. Leonhardt, T.: Familial Hypergammaglobulinaemia and Systemic Lupus Erythematosus, Lancet **2:** 1200, 1957.
39. Nathan, D. J., and Snapper, I.: Simultaneous Placental Transfer of Factors Responsible for L. E. Cell Formation and Thrombocytopenia, Am. J. Med. **25:** 647, 1958.
40. Holman, H., Deicher, H., and Kunkel, H.: Unpublished results.
41. Moore, J., and Lutz, W.: Natural History of Systemic Lupus Erythematosus: An Approach to Its Study Through Chronic Biologic False Positive Reactors, J. Chron. Dis. **1:** 297, 1955.
42. Muehrcke, R., Kark, R., Pirani, C., and Pollack, V.: Lupus Nephritis, Medicine **36:** 1, 1957.
43. Heller, B. I., Jacobson, S. E., and Hammersten, J. F.: Effect of Cortisone (Adrenocortical Preparation) in Glomerulonephritis and Nephropathy of Disseminated Lupus Erythematosus, J. Lab. & Clin. Med. **37:** 133, 1951.
44. Soffer, L. J., and Bader, R.: Corticotropin and Cortisone in Acute Disseminated Lupus Erythematosus; Results of Long-Term Use, J. A. M. A. **149:** 1002, 1952.
45. McCombs, R., and Patterson, J.: Factors Influencing the Course and Prognosis of Systemic Lupus Erythematosus, New England J. Med. **260:** 1195, 1959.
46. Holman, H., and Deicher, H.: Unpublished results.
47. Pollack, V., Pirani, C., Kark, R., and Muehrcke, R.: Effect of Large Doses of Prednisone on Renal Lesions of Lupus Glomerulonephritis, Clin. Res. **7:** 285, 1959.
48. Kierland, R. R., Brunsting, L. A., and O'Leary, P. A.: Quinacrine (Atabrine) Hydrochloride in Treatment of Discoid Lupus Erythematosus, A. M. A. Arch. Dermat. & Syph. **68:** 651, 1953.
49. Parker, F., and Irvin, J.: The Interaction of Chloroquin With Nucleic Acids and Nucleoproteins, J. Biol. Chem. **199:** 897, 1952.
50. Joske, R. A., and King, W. E.: "L. E.-Cell" Phenomenon in Active Chronic Viral Hepatitis, Lancet **2:** 477, 1955.
51. Bearn, A. G., Kunkel, H. G., and Slater, R. J.: Problem of Chronic Liver Disease in Young Women, Am. J. Med. **21:** 3, 1956.
52. Mackay, I. R., Taft, L. I., and Cowling, D. C.: Lupoid Hepatitis, Lancet **2:** 1323, 1956.
53. Bartholomew, L. G., Hagedorn, A. B., Cain, J. C., and Baggenstoss, A. H.: Hepatitis and Cirrhosis in Women With Positive Clot Tests for Lupus Erythematosus, New England J. Med. **259:** 947, 1958.

CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S MEDICAL CENTER, BOSTON, MASS.

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THIS white girl was born after a 40 week gestation and weighed 6 pounds, 13 ounces. Soon after birth, cyanosis and a heart murmur were discovered.

The family history is of interest in that the father and paternal grandmother had congenital hemolytic anemia. A paternal aunt and the maternal grandmother had undergone cholecystectomy. The paternal grandmother had several miscarriages, and several of her children died in early infancy.

The patient was first admitted to The Children's Hospital at the age of 2 years, 3 months, with a diagnosis of convalescent poliomyelitis. At this time hyperreflexia of the upper extremities and absent reflexes in the lower extremities were noted. Hepatosplenomegaly and hemorrhoids were also observed, and the history revealed that these had been present for 3 to 4 months.

The peripheral platelets, leukocytes, and erythrocytes were all decreased, but there was normal maturation of the red and white cells. The megakaryocytes were decreased in number and there was no evidence of platelet formation. The serum thymol flocculation, thymol turbidity, and cephalin flocculation tests for liver disease were abnormal.

Owing to persistently low platelet levels and bleeding gums, a splenectomy and liver biopsy were performed. Pathologically, the spleen was characterized by perisplenitis and fibrinous granulomatous reactive centers, without evidence of hypersplenism. She was discharged with the thrombocytopenia unrelieved.

One month after the operation, at 2 years, 4 months, she entered the hospital with a diagnosis of pneumococcal meningitis. The platelets were now normal.

Six months after this, at the age of 2 years, 10 months, she was admitted with a fever of unknown origin, with the development of a diffuse, nodular, pulmonary infiltrate not responding to antibiotics, and a congenital heart lesion not further diagnosed.

A month later, on her fifth admission, because of dry cough, anorexia, increasing cyanosis, and marked exertional dyspnea, a cardiac catheterization was carried out. This demonstrated a pulmonic infundibular and valvular stenosis, a right-to-left shunt at the ventricular level, and mild pulmonary hypertension, the pulmonary wedge pressure being elevated. A diagnosis of tetralogy of Fallot was made on the basis of these findings. A lung biopsy displayed marked intimal proliferation and thickening of the arterial walls, consistent with pulmonary hypertension. Digoxin was started at this time.

The next two admissions at one month intervals followed spontaneous subarachnoid hemorrhages. The first gave rise to a partial right hemiplegia.

She returned within a week after dis-

charge because of irritability, anorexia, and apathy. On admission, respirations were shallow and 66 per minute, but the other vital signs were normal. The child was irritable and spastic and she had an ophthalmoplegia. The fundic vessels were tortuous and a hemorrhage was seen in the left eye. A few scattered râles were heard at the left lung base. The left cardiac border was 2 cm. within the anterior axillary line. The heart impulse was diffuse but maximal at the left lower sternal border. No thrill was detected, but a Grade III harsh blowing systolic murmur, maximal at the left lower sternal border, was heard over the entire precordium and in the back. The pulmonary second sound was decreased. The smooth liver edge was 5.0 cm. below the costal margin. Bilateral positive Babinski signs and right knee and ankle clonus could be elicited. The femoral pulses were strong and synchronous with the radial.

The urine and blood examinations were negative except for a mild anemia. Roentgen studies showed an enlarged heart. The lungs were irregularly hyperventilated with a less flocculent but persistent density, as seen in previous films. These were thought to represent arterial disease with changes due to repeated pulmonary infection. The electrocardiogram was interpreted as showing an incomplete right bundle block and right ventricular hypertrophy, abnormal for the age.

The patient was given physiotherapy, Digoxin, and antibiotics. She appeared to be improving slowly, but 5 weeks after admission she suddenly developed a fever of 107° F., a watery diarrhea, increased cyanosis, and labored respirations, and she died.

DR. ALEXANDER S. NADAS.* I will say at once that I know more about this child than appears in the protocol. I saw her at the age of 3½ months when, on the basis of physical findings, electrocardiogram, and roentgen examination, I made the tentative diagnosis of tetralogy of Fallot. If I could close the discussion there, I would be 100 per cent correct. I saw her again in another hospital at the age of 13 months because of what I interpreted to be an anoxic spell of tetralogy of Fallot. She was slightly anemic at this time, secondary to the cyanosis, so she was placed on iron therapy.

By the age of one year, 4 months, the diagnosis of tetralogy of Fallot was clear-cut. Trespassing beyond the limits of cardiology, I examined the abdomen and found the spleen to be enlarged to the iliac crest, but the liver was only 4.0 cm. below the costal margin. I then elicited the history from the father that he, his brother, and his father all had large spleens and had been told they had congenital hemolytic anemia. This was substantiated, but the child was found to have normal erythrocytic fragility and no increase in spherocytes, so she was considered not to have familial spherocytic anemia. All this took place before the child's hospital record started.

At the time of her first discharge from the hospital, she was thought to have portal hypertension.

A splenectomy was performed because of the persistently low platelet levels.

Dr. Schuster, would you tell us the operative findings?

DR. SAMUEL R. SCHUSTER. No portal vein pressures were taken at operation, but there was no engorgement or enlargement of the splenic vein.

DR. NADAS. How reliable is direct observation of this sort in assessing the presence or absence of portal hypertension?

DR. SCHUSTER. In view of the presence of a spleen of this size, if the enlargement were the result of portal hypertension I think there would be a very large engorged splenic vein. The situation would be difficult to misinterpret in this instance.

DR. NADAS. The protocol says no evidence of hypersplenism was found. I presume this was opinion based on anatomical criteria. Dr. Craig, would you explain the significance of this statement?

DR. CRAIG. One of the few criteria we have, pathologically, for the presence of

*Dr. Nadas is Assistant Clinical Professor of Pediatrics, Harvard Medical School, and Cardiologist to The Children's Hospital.

hypersplenism is the presence of the so-called "inside-out follicle." This consists of a rim of immature cells surrounding an inner mass of more mature cells of the Malpighian follicle. This is a finding in a high percentage of patients with primary or functional hypersplenism. This is not an infallible sign. It is a finding independent of congestion, though it may also be found in congestive splenomegaly where an element of hypersplenism may be present.

Dr. Nadas. I will assume, then, that the spleen did not reveal evidence of congestive splenomegaly nor the usual appearance of functional hypersplenism. The removal of the spleen did not cause a sharp rise in the platelet count, as might be expected with hypersplenism.

The third admission was for pneumococcal meningitis; this appears now to be a recognized hazard in children who have splenectomy. Dr. Craig, could you tell us how frequent this sequence of events is?

Dr. Craig. Our incidence is 5 to 10 per cent of severe sepsis, often pneumococcal, following splenectomy, particularly in the younger children.

Dr. Nadas. So, this represents a hazard which must be taken into account with the expected benefits from splenectomy in children. At any rate, the platelets soon returned to normal. The removal of the spleen, followed by the antigenic stimulation of an infection, thus restored the platelet level. I wonder why Digoxin was started?

Dr. Michael Braudo. She was thought, on the basis of pulmonary signs and roentgen findings, to be in left-sided failure.

Dr. Nadas. That is a very unusual complication for a patient with tetralogy of Fallot, especially in infancy. May we now see the x-rays, Dr. Neuhauser?

Dr. E. B. D. Neuhauser. The initial films all have similar silhouettes, with right ventricular dominance, a "sabot" contour, and a small left ventricle. The pulmonary artery could not be seen well at fluoroscopy, and the waist was not as concave as in many cases of tetralogy. The aorta was prominent on the left, and the vena cava on the right side. The pulmonary vasculature on the left is diminished in prominence, but on the right this is barely abnormal.

During several episodes of respiratory infection, increases in the lung densities occurred, but I do not believe we ever made a roentgen diagnosis of congestive heart failure.

Six months after the pneumonia, the picture changed entirely. Small rounded shadows appeared, chiefly on the right side, and less on the left, which tended to become confluent (Fig. 1). They were more striking about the base of the heart, where the mediastinal shadow broadened out. These nodose infiltrations became less prominent toward the end of the patient's life.

Dr. Nadas. I must assume then that this lung lesion has nothing to do with the heart lesion of tetralogy of Fallot, or that my diagnosis of the heart malformation is wrong, and that this lung picture is associated with increased pulmonary venous pressure of mitral stenosis or left-sided failure.

Dr. Neuhauser. These lesions are not consistent with pulmonary edema of heart failure but are small, rounded nodose lesions. We would consider their origin related to tumor infiltrations, vascular lesions, or granulomas.

Later in her course, while the larger lesions remained unchanged, a large number of new small, rounded shadows became superimposed on the prominent changes in

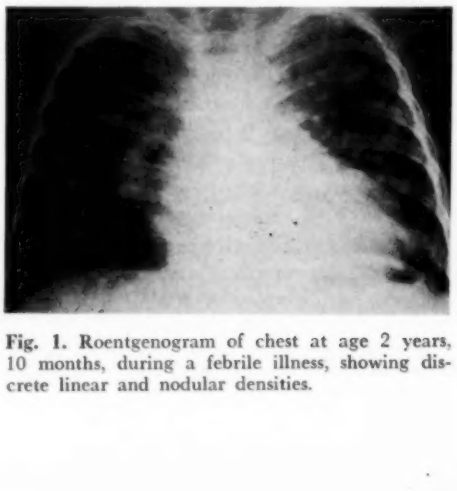

Fig. 1. Roentgenogram of chest at age 2 years, 10 months, during a febrile illness, showing discrete linear and nodular densities.

Fig. 2. Photomicrograph of the lung. The pulmonary vessels have a marked thickening of the wall, due chiefly to proliferation of the intima. (Toluidine blue and eosin. ×110; reduced ⅕.)

the hilar area. The spleen and liver were enlarged initially and remained so throughout her course.

We would concur in your diagnosis of tetralogy of Fallot from a roentgenologist's point of view.

DR. NADAS. We note, on her final summary, that the patient had a hemoglobin level of 11.0 Gm. In a cyanotic child, this represents a significant anemia. Dr. Byers, what do you consider the central nervous system disease represents?

DR. RANDOLPH K. BYERS. The description is that of a child with very widespread involvement of the cortex. The reactivity of the pupils indicates that the intracranial pressure is not high. A venous thrombosis could do this; such cases in children are often diagnosed as having spontaneous subarachnoid hemorrhage, but later become decerebrate.

DR. NADAS. Dr. Craig, could you tell me a little more about the lung biopsy specimen—did it resemble the change we see in pulmonary hypertension, or that seen with an obstructive lesion at the left atrial level?

DR. CRAIG. The lesion in this biopsy was in vessels of a larger caliber than we usually see in pulmonary hypertension associated with congenital heart disease with left-to-right shunt, being in vessels with definite muscular walls; it did not have the obliterative features of that process. It was even less similar to the lesions seen in cases of mitral stenosis which are chiefly in the precapillary arterioles (Fig. 2).

DR. NADAS. There are a number of features in this case that must be explained; these include the anemia, the thrombocytopenia which continued in spite of a splenectomy, the pulmonary lesion, the repeated bouts of febrile illness, and the hepatosplenomegaly.

The anemia is not due to lack of red blood cell production, since an active bone marrow was demonstrated on aspiration; nor was there any recorded evidence of blood loss. There is more evidence that this is an anemia of blood destruction. The patient's race would make sickle cell anemia unlikely. The Moschcowitz syndrome may give anemia and thrombocytopenia, but this is a much more rapidly progressing disease than we have here.

Fig. 3. The heart. At the arrows are the dilated, greatly thickened coronary arteries.

I do not believe the hepatomegaly is due to congestion or to cirrhosis. The possibility of a disease of the reticuloendothelial system, such as Letterer-Siwe disease, must be considered in view of all the findings in the liver, spleen, and lungs mentioned above.

What type of infection could produce such a picture? Endocarditis might arise this early and persist for over a year, with emboli being thrown off to various sites. This is more commonly seen in adults than in children. Other more exotic infections, such as histoplasmosis, might be suggested.

Periarteritis nodosa should be mentioned in the differential diagnosis, but I have little on which to base that diagnosis. The best diagnoses that I can make are tetralogy of Fallot and a superimposed infectious process, perhaps with an endocarditis.

DR. CRAIG. Someone has suggested that pulmonary arterial lesions associated with pulmonary hypertension might be seen in the tetralogy of Fallot.

DR. NADAS. Dr. Arnold Rich demonstrated, long ago, that one might have thrombotic lesions in the pulmonary circulation in older, intensely polycythemic patients with tetralogy of Fallot, but never at this age. This child never had a marked polycythemia, or even very low oxygen saturation.

DR. CRAIG. This patient is not one of those with an Eisenmenger complex early in life who develops a progressive pulmonary stenosis, which has been emphasized by Dr. Gasul and his colleagues?

DR. NADAS. This may be a changing pattern in some patients, but in this child there was never any evidence, by roentgen changes of pulmonary plethora, of a left-to-right shunt, nor was there a diastolic rumble. Throughout the course, I think pulmonary stenosis was the dominant lesion.

DR. NEUHAUSER. A paper from Stockholm[1] recently reported lungs in which were found numerous areas of pulmonary artery stenosis with accompanying zones beyond those of poststenotic dilatation. On x-ray examination, the lungs did not seem to be too different from these.

A PHYSICIAN. Dr. Neuhauser, do you believe that this picture could be mimicked by idiopathic pulmonary hemosiderosis?

DR. NEUHAUSER. No.

DR. NADAS. Might these rounded shadows in the lung, then, represent small aneurysms? Do you believe that the vascular alterations in the lung could be related to the intracranial hemorrhage?

DR. NEUHAUSER. I do not believe that the changes in the lungs are on the basis of heart disease. I assume the patient had a similar vascular disturbance elsewhere.

DR. GORDON F. VAWTER. This patient did have, at autopsy, a congenitally deformed heart of the tetralogy of Fallot type which had a considerable degree of right ventricular hypertrophy and dilatation. The outflow tract had a prominent *crista supraventricularis*.

The coronary vessels were markedly tortuous and nodose (Fig. 3). The walls in the nodose areas were greatly thickened, with almost total obliteration of the lumen by intimal proliferation. These areas had a minimal inflammatory infiltration. The elastic tissue was grossly interrupted in the internal lamella (Fig. 4).

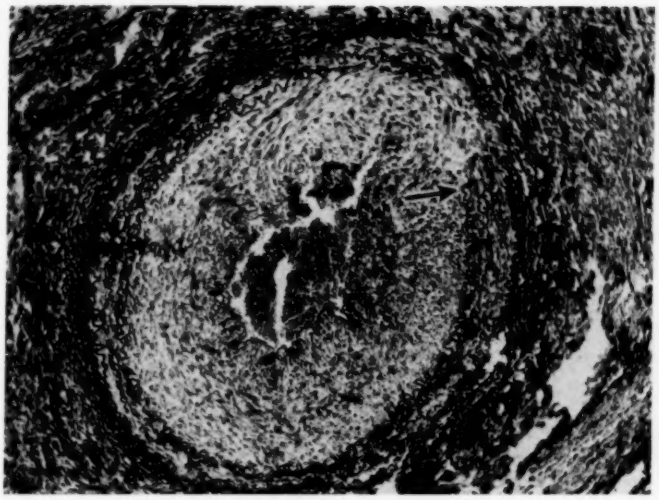

Fig. 4. Photomicrograph of the heart. A cross section of the coronary artery emphasizes the marked aneurysmal dilatation of the vessel and its partial occlusion by the proliferation of the intimal tissue. At the arrow is the old interrupted internal elastic membrane. (van Gieson–elastic tissue. ×110; reduced ⅕.)

Fig. 5. The lung. A cross section of the fixed lung specimen is punctuated by the elevated and markedly thickened pulmonary arteries.

In the lung, the vessels of large caliber had the same features as the coronary vessel, with a thin irregular media, a massive intimal proliferation, and little evidence of thrombosis, necrosis, or inflammation. The large "pipestem" arteries protruded above the cut surface of the lung (Fig. 5). Except for dense lymphoid infiltrations in the peribronchial regions, the lungs were not otherwise remarkable.

Though in the liver biopsy no vascular lesions were present, only small periportal lymphoid alterations being seen, in the liver at autopsy there were conspicuous focal vascular lesions, basically similar to those in the coronary vessels, with total obliteration and apparent recanalization of the lumen. No scarring or infarction resulted from these.

Similar lesions were present in the renal vessels at the hilus of the kidney (Fig. 6), in the mesenteric arteries, in the periadrenal fat, in the brain, in the intercostal and internal mammary arteries, and in other viscera. In the brain, the oldest lesion was in the insula—a hemosiderin-laden mass of necrotic tissue which was interpreted as an anemic infarct complicated by subsequent

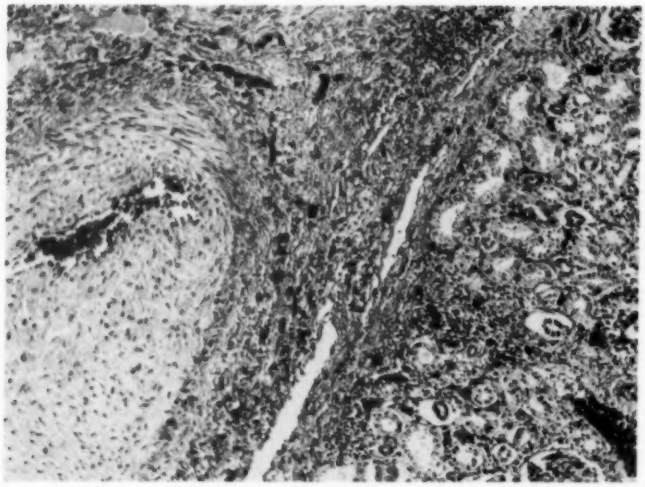

Fig. 6. Photomicrograph of the kidney. At left is a large, nearly occluded artery of the kidney. (Hematoxylin and eosin. ×130; reduced ⅕.)

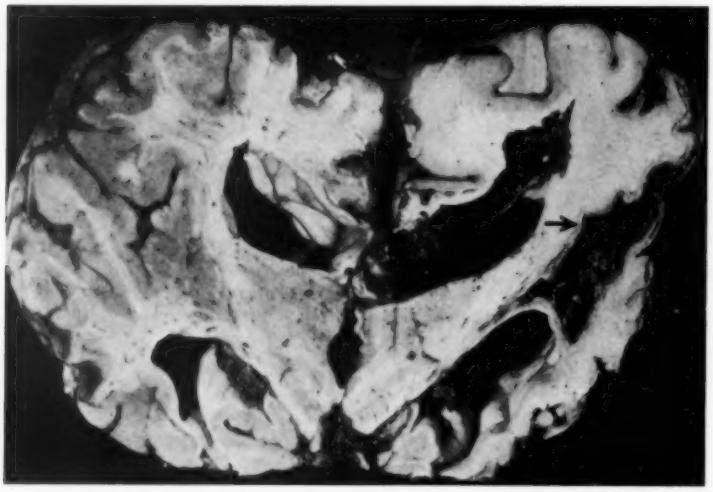

Fig. 7. A cross section of the brain showing atrophy of the parietal paracentral gyrus on one side and the insula and temporal lobe on the opposite side. Thickened gaping middle cerebral vessels are present at arrow.

hemorrhage. On both sides of this lesion there was extensive necrosis of the cortex associated with arterial lesions, as previously described (Figs. 7 and 8). It seems probable that the decerebrate state of the patient was related to this lesion. No lesions in the major vessels at the base of the brain were found, although there was a saccular aneurysm of the basilar artery.

We have seen this type of coronary artery disease in 3 patients under one year of age; one of these was a newborn infant. Similar cases have been described in the recent literature.[2] In none of these has there been

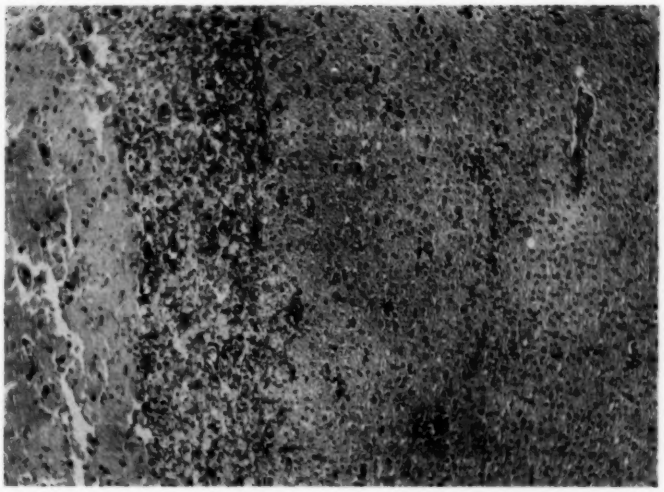

Fig. 8. Photomicrograph of the brain. At left, atrophic necrotic brain separated by a dense gliotic zone from relatively normal white matter. (Hematoxylin and eosin. ×130; reduced ⅕.)

involvement of the pulmonary vasculature.

Most authors place these lesions in the category of polyarteritis, though in this case there is a conspicuous lack of infarction or organ atrophy, except in the brain. The other possibility is that there is a congenital aneurysm with secondary thrombosis, especially since 2 of these in our group have been associated with congenital pulmonary stenosis.

DR. JOHN F. CRIGLER. Were any abnormalities in the blood vessels seen in the surgical specimens of the liver or spleen?

DR. CRAIG. No, none were seen. However, there was no real infundibular stenosis. The pulmonary valve was bicuspid and had a circumference of 3 cm., which is only slightly under the normal value for the age. The ductus arteriosus was barely patent. The ventricular septal defect was 1 cm. in diameter. The left ventricular wall also was slightly hypertrophied. There was no evidence of bacterial endocarditis or mural thrombosis or myocardial necrosis.

We believe that aside from the tetralogy of Fallot, a *healed polyarteritis with aneurysm formation* is the best diagnosis here. The acute stage probably took place during the episode of fever, and the flocculent appearance in the roentgenograms of the lungs occurred shortly afterward. The lung lesions subsequently became less flocculent and more dense.

We have no good explanation for the hepatomegaly nor for the early splenomegaly and thrombocytopenia, unless they are a part of the general disturbance, the most obvious manifestation of which is the polyarteritis. Some degree of passive congestion remained in the liver, which might explain the terminal persistence of its enlargement.

REFERENCES

1. Gyllenswörd, Å., Lodin, H., Lundberg, Å., and Möller, T.: Congenital Multiple Peripheral Stenoses of the Pulmonary Artery, Pediatrics **19:** 399, 1957.
2. Crocker, D. W., Sabin, S., and Thomas, W. C.: Aneurysms of the Coronary Arteries; Report of Three Cases in Infants and Review of the Literature, Am. J. Path. **33:** 819, 1957.

COMMENTS ON CURRENT LITERATURE

Sex-chromatin pattern in a case of hemophilia

CLASSICAL hemophilia, antihemophilic globulin deficiency, called in recent publications type A, follows in inheritance a distribution compatible with that of determination by a sex-linked recessive gene. Thus the condition would be expected to be very uncommon in females. The accepted genetic situation for its occurrence in the female is the fertilization of an ovum carrying in the X-chromosome a recessive hemophilic gene by a sperm also carrying the defective gene in its X-chromosome, resulting in an individual homozygous for this recessive. The discovery in 1948 by Hutt, Rickard, and Field[1] of a female dog showing a bleeder's disease which appeared to be identical with hemophilia in the human subject stimulated experimental investigations of the disease in dogs. Brinkhous, and Graham, and their associates[2] were able to study the disease in female pups occurring among litters from the mating of a hemophilic male with a carrier female.

The human counterpart of this mating is possible, and such a female bleeder having a carrier mother and a hemophilic father was reported by Israëls, Lempert, and Gilbertson[3] in 1951. Their patient had a clinical history and the laboratory findings characteristic of true hemophilia. This family is of considerable interest since the occurrence of bleeder's disease is well documented in the genealogy on both sides, with no known consanguinity between the 2 family lines. The patient's father was a known hemophiliac with a lifelong history of easy bruising, recurrent hemarthrosis, and hematuria. The father's brother, also a known bleeder, had recurrent critical episodes of hemorrhage following minor trauma; the father's sister had 2 sons who were not affected. The patient's mother must be presumed to be a carrier; the mother's brother was known to have hemophilia with a history of recurrent hemarthrosis; he died in the hospital from severe hemorrhage following an accident. The mother's sister is presumed to be a carrier since she has a son with classical hemophilia. The patient's daughter, less than 1 year of age at the time of the reporting, is also presumed to be a carrier.

Several other cases of true hemophilia in women have been described in the literature. Merskey[4] reported in 1951 a follow-up study on an interesting hemophilic family first described by Treves in 1886. This family was in the seventh generation in 1951. Following a first-cousin marriage in the fourth generation, 6 of 12 children had classical hemophilia, 3 of whom were females. In 2 other recorded cases[5] in women, the coagulation defect was indistinguishable from classical hemophilia type A, yet no positive family history for hemophilia or other bleeding tendency could be elicited. These deviations from the strict genetic pattern of sex linkage are difficult to account for, and the possibility of mutation has been discussed.

Recent interest in chromosomal patterns in man has opened the way to another ex-

planation which may account genetically for some of these deviations from the expected distribution of sex-linked traits. In a recent issue of *Lancet,* a case of severe hemophilia A in a girl has been described in which chromosomal studies explained the apparent exception from sex-linked inheritance. The child, whose "external genital characteristics were female, was shown to have a male sex-chromatin pattern." This report is by Nilsson, Bergman, Reitalu, and Waldenström,[6] a group of investigators and clinicians at the University of Lund, Sweden. The patient, a child of 16 months, had always bruised readily. At the age of 12 months, trivial trauma of the thigh resulted in a large hematoma for which hospitalization was required. At this time prolonged coagulation time was noted. On a later occasion she experienced another large hematoma; on this occasion the hemoglobin fell from 11.2 Gm. per 100 ml. to 4.6 Gm., and repeated blood transfusions were required. Previous to this admission she had had episodes of prolonged epistaxis; there had been no bleeding into the joints, but the child had not yet learned to walk. Inquiry into the family history revealed that one of the patient's brothers had died from hemorrhage soon after birth. There was no consanguinity between the parents. None of the paternal ancestors had experienced any bleeding tendencies; the father's coagulation time, bleeding time, and plasma antihemophilic globulin (AHG) were normal. The patient's mother belonged to a hemophilic family which had been studied in 1944 by Sköld.[7] The mother and her maternal cousin, who had a hemophilic son, showed AHG activities of 25 per cent and 35 per cent, respectively. Some other female members of the family thought to be possible carriers showed reduced AHG activity. No congenital malformations were known among the paternal or the maternal ancestors.

On admission to the hospital at 16 months of age, the patient showed several hematomas, but no petechiae. No congenital malformations such as digital anomalies or webbed neck were observed. Physical and roentgenographic examination did not reveal any evidence of heart malformation. While the external genital characteristics were female in appearance, the labia minora were small and the clitoris somewhat large for a child of this age. No uterus could be palpated per rectum and the hymen appeared to be imperforate. Exhaustive coagulation and other hematologic studies gave results which indicated that this patient was suffering from a hemorrhagic disorder identical with severe hemophilia A in males. Cytogenetic studies included sex determination by morphology of cells seen on blood films, and studies of resting cells from skin specimens, both of which suggested a male sex pattern. Bits of skin, epidermis only, were cultured by the method of Reitalu and Bergman.[8] Epithelium-like cells grew out very gradually, and on final transfer to slides the mitotic frequency was still low. Nevertheless some satisfactory preparations were obtained, exposed to colchicine, fixed, and stained. Cells in metaphase showed 46 chromosomes, 22 pairs of autosomes, one normal-appearing X-chromosome and a small chromosome, apparently a Y-chromosome.

In attempting to evaluate these findings, the authors considered 3 possibilities: "the child might be a homozygous haemophilic female by inheritance or by mutation; the child might be a heterozygous female (carrier) with unusual bleeding tendency; or . . . might have a male chromosomal pattern."[6] Turner's syndrome and a possible XO type female seem unlikely in this case. On the basis of the sex-chromatin and chromosomal patterns, the authors are inclined to regard this child as a potential male, possibly a hermaphrodite or an individual in whose embryonic development some hormonal influence, or other irregularity in ontogenesis, brought about feminization. The child's age makes exact anatomical sex determination difficult except by gonadal studies. As the authors suggest, continued study of this child's development will be of considerable interest.

At the present time sex-chromatin patterns in intermitotic nuclei and chromosomal con-

figurations of dividing cells in human tissues are assuming importance as useful aids in diagnosis and in attempts to understand certain clinical conditions. A recent issue of *Science* carries a very informative article by Murray L. Barr[9] whose interest in this field is of long standing. This article, which is based in part on The Lecture in Medicine given before the Royal College of Physicians and Surgeons of Canada in January, 1959, comprises a series of brief discussions covering normal gonadal differentiation, normal differentiation of internal and external genitals, sex dimorphism of the intermitotic nucleus, early masculinization or feminization, gonadal dysgenesis, and the like. In the course of these discussions Barr states, "Chromosomal, gonadal, and phenotypical sex are normally in agreement. But the sex-chromosome complement may be inconsistent with the main features of the phenotype when there has been an error in gonadal differentiation. . . . The important significance of the recent observations on chromosomal abnormalities is the clear demonstration of aneuploidy as a cause of some developmental errors in man. The next few years are certain to bring developments of the first importance in the field of human cytogenetics, and in the application of cytogenetics to certain aspects of clinical medicine."[9]

RUSSELL J. BLATTNER

REFERENCES

1. Hutt, F. B., Rickard, C. G., and Field, R. A.: Sex-linked Hemophilia in Dogs, J. Hered. **39:** 3, 1948.
2. Brinkhous, K. M., and Graham, J. B.: Hemophilia in the Female Dog, Science **111:** 723, 1950.
   Brinkhous, K. M., Graham, J. B., Penick, G. D., and Langdell, R. D.: Studies on Canine Hemophilia, Trans. Fourth Conference on Blood Clotting and Allied Problems, New York, 1951, Josiah Macy, Jr. Foundation.
3. Israëls, M. C. G., Lempert, H., and Gilbertson, E.: Haemophilia in the Female, Lancet **1:** 1375, 1951.
4. Merskey, Clarence: The Occurrence of Hemophilia in the Human Female, Quart. J. Med. **20:** 299, 1951.
5. Choremis, K. B., Zervos, N., Tsevrenis, H., Apostolopoulou, E., and Mandalaki, T.: Hémophilie A chez une fille âgée de deux ans, Helvet. paediat. acta **11:** 305, 1956.
   Quick, A. J., and Hussey, C. V.: Haemophilia-like States in Girls, Lancet **1:** 1294, 1958.
6. Nilsson, I. M., Bergman, S., Reitalu, J., and Waldenström, J.: Haemophilia A in a "Girl" With Male Sex-Chromatin Pattern, Lancet **2:** 264, 1959.
7. Sköld, Erik: On Haemophilia in Sweden and Its Treatment by Blood Transfusion, Acta med. Scandinav. Supp. **150:** 73, 1944.
8. Reitalu, J., and Bergman, S.: Acta path. et microbiol. Scandinav., 1959. In press, see Ref. 6.
9. Barr, M. L.: Sex Chromatin and Phenotype in Man, Science **130:** 679, 1959.
   Grumbach, M. M., and Barr, M. L.: Cytologic Tests of Chromosomal Sex in Relation to Sexual Anomalies in Man, in Pincus, Gregory, editor: Recent Progress in Hormone Research, III. Aspects of Reproduction, New York, 1958, Academic Press Inc., vol. 14, p. 255.

Correspondence

To the Editor:

Can you acquaint me with an experienced pediatrician who has developed a pattern of practice over the years based on the philosophy of long-term planning?

In order to counteract the boredom of daily routine, in order to develop a purposeful plan for a lifelong pediatric practice, so that one may see some sort of goal to shoot for, and also in order to provide more sound care for patients with long-term troubles, I am interested in knowing what other men have done in the planning of their own practices.

For instance: Has anyone been able to work out successful weight control programs for teenagers, with or without group meetings, and have they been followed up with any system, by either letters or calls? Have pediatricians in private practice utilized small clinics or group meetings for following patients with diabetes, and especially with epilepsy, with or without letter follow-up for those who are reluctant to come in frequently? Is there any worthwhile plan for following up patients apparently cured of recurrent pyuria, and should it include repeated x-ray studies, urinalyses, urine cultures, or simply questionnaires? Has any philosophy been devised for the follow-up of patients who have been found to have hypogammaglobulinemia with apparent recovery (having been supported by gamma globulin injections)? What do other men do in the matter of following patients with rheumatic heart disease beyond their prophylaxis, respiratory infections, and periodic (annual) heart examinations? Have those who practice general pediatrics been able to utilize allergy "clinics" similar to those used in our medical centers and by men practicing straight allergy? Is the response better, working with individual patients, or with the group (discussion) approach? What can we do in addition to holding weekly discussions on prevention of accidents and injuries at our well-baby clinics, talks at PTA meetings, and dissemination of brief, attractive literature for control of this problem?

And are there other projects that I simply have not recognized that warrant year-round attention?

SAM POBANZ, M.D.
ONTARIO, OREGON

It is hoped that several "experienced pediatricians" will share their experiences with Dr. Pobanz, especially in relation to the values of group activities in private practice with children who have a particular medical problem in common.

EDITOR

Books

Clinical Auscultation of the Heart.
Samuel A. Levine, M.D., and W. Proctor Harvey, M.D., Philadelphia, 1959, W. B. Saunders Company, 657 pages. Price $11.00.

This is a well-written and well-illustrated text on clinical auscultation of the heart. However, it is written mainly from an adult standpoint and illustrated with adult phonocardiograms and electrocardiograms. In the chapters on general subjects, such as normal heart sounds, there are few references to differences in the pediatric age group and the difficulties encountered in auscultating infants and young children.

The one section on cardiac murmurs in congenital heart disease is illustrated with material from children since these congenital lesions are found more frequently in the pediatric age group. Since descriptions of the clinical patterns other than those obtained from auscultation are presented the material is interesting and informative.

C. ROBERT E. WELLS, M.D.

Anesthesia for Infants and Children.
Robert M. Smith, M.D., St. Louis, 1959, The C. V. Mosby Company, 409 pages. Price $12.00.

There has long been a need for a compilation of the special knowledge of pediatrics, surgery, anatomy, physiology, and pathology of value to those who administer anesthesia to infants and young children. This new text on pediatric anesthesia discusses every phase of the subject thoroughly and extensively.

The book is written essentially with two purposes in mind: The first is to supply information in the basic sciences as it relates to infants and children. Particularly excellent is the chapter, "Respiratory Physiology in Infants and Children," by Charles D. Cook, M.D.

The other purpose is to discuss in detail the preparation and management of anesthesia from the time the surgeon schedules the operation until the patient has become a hospital statistic (good or bad). This includes preoperative evaluation, psychological preparation, choice of anesthetic agents and techniques, management during operation, and postoperative complications. The extensive lists of references at the end of each chapter include almost every text and paper of value in the respective subjects.

The author, in his enthusiasm for minute detail, has unnecessarily complicated the schedules of premedication with various drugs and the listing of multiple tables. In Table 11, "Laryngoscopes Recommended for Use in Infants and Children," no fewer than eight different instruments are listed for various age groups. This is patently unnecessary even for the most specialized pediatric anesthesiologist. In Table 13, "Recommended Agents and Techniques for Specific Operations," another unnecessary list states that an adult circle apparatus may be used on a child weighing 35 or more pounds. This is contrary even to the author's teaching of pediatric anesthesia.

Despite the superfluous tables, however, the author has compiled for the first time in a single text a wealth of information relating to pediatric anesthesia. The text is of special value to those in training in anesthesiology and to those who have the responsibility for the care of an infant or child during operation: the pediatrician, pediatric surgeon, and pediatric anesthesiologist.

JACOB B. FRIEDMANN, M.D.

Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome.

Jack Metcoff, M.D., Editor, New York, 1959, The National Kidney Disease Foundation, 282 pages.

Each year for three consecutive days a group of people gather around a conference table to discuss the problems related to renal disease in children. These meetings are relatively small in terms of participants but each year there is found some "new blood" present to help maintain the stimulating atmosphere.

The subject matter covered at each conference is vast, but each topic has some relationship to the kidney. In this, the tenth conference, the majority of the space is devoted to renal change observed by histochemical techniques and by light and electron microscopy. Experimental and human renal disease is discussed at length. The remaining pages are devoted to discussions of therapeutic approaches to the patient with nephrosis and to the annual estimates of prognosis as observed in this disease in various medical centers throughout the world.

The mode of presentation is informal and yet quite didactic. The illustrations are clear and informative. This is an indispensable publication for any reference library and for those with especial interest in renal disease.

DANIEL FLEISHER, M.D.

Diseases of Children in the Subtropics and Tropics.

H. C. Trowell, O.B.E., M.D., F.R.C.P., and D. B. Jelliffe, M.D., M.R.C.P., D.C.H., D.T.M.&H., London, 1958, Edward Arnold & Co., Ltd. (The Williams & Wilkins Co., Baltimore, Md., exclusive U. S. agents), 919 pages, 181 illustrations. Price $18.50.

This is the first textbook in English designed to present the problems of children in the tropics and subtropics. Drs. Trowell and Jelliffe, along with seventy-two collaborators, describe with clarity the many diseases common in the areas where more than half of the world's children live.

This text has been prepared for students and physicians who are concerned with children in the tropics and subtropics. Accordingly, this book will have limited usefulness to pediatricians in this country and in other areas in the temperate zones. However, physicians who are curious to learn "how the other half lives" will find that this text contains a tremendous amount of stimulating reading, especially regarding infectious diseases and nutritional problems. The impact of tribal customs and other local cultures on child welfare will be of interest to many.

This text should be a valuable reference book for those physicians who occasionally see children who have lived in the tropics. It should be of interest to those who have a broad concern in all pediatric problems.

ROBERT H. HIGH, M.D.

News and notes

A fellowship in renal research will be available beginning July 1, 1960, in the **Department of Pediatrics, Western Reserve University School of Medicine.** The candidate would be expected to spend approximately two thirds of his time in laboratory research and one third in clinical work with patients under investigation. Salary will be $5,000 to $5,500. Applicants with minimum training of 2 years in pediatrics and laboratory experience are preferred.

Correspondence should be sent to Walter Heymann, M.D., 2103 Adelbert Road, Cleveland 6, Ohio.

Residencies and traineeships in pediatric hematology are available at the **Childrens Hospital of Los Angeles, Department of Pediatrics, University of Southern California,** including instruction in laboratory procedures and research methods, participation in research, and clinical experience.

Applicants for residencies should have completed pediatric training acceptable for certification by the American Board of Pediatrics. The stipend is $3,300 per annum.

The traineeship is a two-year program designed to prepare qualified individuals for academic medicine and research. Applicants should have completed three or more years of training beyond the M.D. or Ph.D. degree. Some previous experience in clinical hematology or a preclinical science related to hematology is desirable. Applications for one year will be considered. The stipend is $5,500 per annum.

Applicants should write to Dr. Denman Hammond, Associate Hematologist, Childrens Hospital of Los Angeles, 4570 Sunset Boulevard, Los Angeles 27, California.

The **Ninth Annual Postgraduate Seminar for Pediatricians** will be conducted at St. Christopher's Hospital for Children, the Pediatric Department of Temple University School of Medicine, Philadelphia, June 1 to 4, 1960. Half-day sessions will be devoted to various phases of pediatric medicine.

For information regarding enrollment, program, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 North Lawrence Street, Philadelphia 33, Pennsylvania.

A number of **Fellowships in Pediatric Endocrinology** are available at salaries of $5,000 to $5,500 per year at the Johns Hopkins Hospital. Such trainees must have completed residencies of two to four years on pediatric house staffs and, preferably, should be interested in academic or research careers. They will be accepted for periods of one or two years' training in pediatric endocrinology. One year will be spent largely in clinical diagnostic and investigative work and the other in laboratory research.

Those interested and qualified may write to Dr. Lawson Wilkins, The Harriet Lane Home, Johns Hopkins Hospital, Baltimore 5, Maryland, sending *curriculum vitae* and letters of recommendation.

The University of Minnesota is holding a continuation course in pediatric neurology for specialists, supported by the Sister Elizabeth Kenny Foundation, at the Center for Continuation Study on the University campus, Feb. 15-19, 1960. It will review general information and evaluate current thoughts in treatment.

Faculty will include Drs. Gilbert B. Forbes, Rochester, New York; Herbert H. Jasper, Montreal; Peter Kellaway, Houston; Richard L. Masland, Bethesda; R. M. Norman, Bristol, England; Carl M. Pearson, Los Angeles; L. Rubinstein, London; Stanley W. Wright, Los Angeles; and faculty members from the University of Minnesota Medical School and the Mayo Foundation.

Lodging and meal accommodations are available at the Center for Continuation Study. For further information write to W. Albert Sullivan, Jr., M.D., Dept. of Continuation Medical Education, University of Minnesota, 1342 Mayo Memorial, Minneapolis 14, Minn.

EDITOR'S COLUMN

Clothes and the man

WITH this issue, as is obvious to even the most casual observer, the JOURNAL appears in a "new suit." The change was not quickly come by. For some 10 or 12 years your Editorial Board has entertained the idea of a new format, but the old seemed comfortable, conservative, and certainly not ostentatious. The JOURNAL since its first issue in 1932 has been received as a friend by the many physicians who care for children and to them it has come to be known as the "gray Journal"—we trust that it will continue so. There were those, however, who thought the gray wasn't very cheering; some even thought it a bit depressing. Others of us thought the cover didn't really matter, except as it was always the same, always readily recognized, always covering dependable information. There are those of us who reluctantly give up an old hat, an old pair of shoes, who don't seem to notice if our favorite, albeit old, suit bags a bit at the knees or even isn't cut to the latest style of Madison Avenue. Such persons do not always wear a new suit with ease and naturalness and, until it is broken in, they feel a bit unnatural, even awkward. We trust our "new suit" will seem to you as it does to us, a bit brighter and cheerier, and that you will recognize beneath this new exterior the same comfortable friendliness, the same sense of responsibility and determination to do all in our power to provide you with useful stimulating pediatric information.

Lest we deny the remnants of the small boy in us, we must confess we like our new suit—and we hope you do too.

Need we say—the years since boyhood have taught us that clothes do not make the man.

Tropical pediatrics

WITH this issue the JOURNAL inaugurates a section on Tropical Pediatrics. The problems of the tropics and subtropics may seem to have little significance to some persons, but to most it is clear that they do indeed have world-wide importance. The time of travel between distant countries is now measured in hours rather than in days and weeks, and interzonal travel has increased proportionately. Immigration from tropical areas is introducing tropical diseases to the temperate zones in quantities not previously experienced. This situation is especially apparent in this country in New York and Philadelphia among recently transported Puerto Ricans. But the principal problems are not those related to travel between countries or of immigration.

The struggles for technical and sociologic improvements are becoming intensified in all of the underdeveloped countries. Health factors loom large. It is axiomatic that sickness breeds discontent, and eradication of malnutrition and control of infection are world-wide problems of the first magnitude among underprivileged peoples. The high birth rates and the excessively high death rates among infants and children emphasize the quantitative aspects.

If world peace is to become a reality, socioeconomic improvements must come first. They will not come without marked decreases in the incidence of nutritional and infectious diseases in the tropical and subtropical areas of the world. Further, there are many possibilities for the study of diseases in the tropical areas which will be applicable to those current in the temperate zones; examples are many and include those related to tuberculosis, poliomyelitis, and a wide variety of problems of undernutrition.

The JOURNAL has been extremely fortunate in securing Dr. D. B. Jelliffe, currently UNICEF Professor of Pediatrics and Child Health at the Medical School of Makerere College in Kampala, Uganda, East Africa, to serve as editor of the section on Tropical Pediatrics. For the past 13 years he has spent most of his time in Africa, India, and Jamaica where he has had first-hand experience with tropical medicine. Original articles to be submitted for publication in this section should be sent directly to him.

Hemorrhagic fever

IN 1951, the United Nations Forces in Korea encountered an acute disease characterized by fever, vomiting, shock, hemorrhagic manifestations and acute renal failure. This disease, completely new to physicians in the Western Hemisphere, was soon recognized to be similar to previous epidemics of hemorrhagic fever reported by Japanese and Russian observers.

It is now interesting to see a report of hemorrhagic fever by Dr. Ethel Nelson from Bangkok, Thailand, in this current issue. This report emphasizes the continued need for consideration of this disease among children in the Eastern Hemisphere where such an illness appears to be presently endemic.

The illness as reported in young adults showed an acute febrile phase during which vomiting and hemorrhagic manifestations occurred. Following this initial period there was a hypotensive phase and a subsequent period of varying degrees of renal damage and failure. The clinical picture described in the children in Thailand differs from the pattern observed in young adults in Korea in the high incidence of respiratory symptoms. The almost complete absence of renal involvement is equally striking since one of the significant problems in the adults was an intense degree of kidney damage. The mortality rate (23 per cent) among the children was much higher in the Bangkok epidemic than that experienced in the United Nations Forces (3 to 4 per cent). The highest number of deaths occurred among the youngest children.

Various epidemics described in the Japanese and Russian studies have shown varying degrees of general symptomatic and system involvement. It does raise the question, however, in the lack of a specific objective diagnostic test at the present, whether all the epidemic hemorrhagic fevers are of similar etiology or of diverse origins. This latter possibility would explain the differences in the clinical patterns. The lack of cases seen in the adult population raises the question as to whether there is specific immunity among the adult population.

Dr. Nelson's report certainly should encourage other physicians caring for children in Asia to look for this illness and to con-

tinue the important investigations into etiology. For physicians in the Western Hemisphere this disease does not present a problem of diagnosis or treatment; however, the varied and intense biochemical and physiologic derangements found in epidemic hemorrhagic fever provide many parallels and lessons for the study of more familiar diseases. The Korean experience in the United Nations Forces certainly led to new concepts of the reactions of the body to an acute infectious process and concerning the sequelae in the kidney and in other areas.

GIULIO J. BARBERO, M.D.

Lectureship program for 1960

EARLY in November The Journal of Pediatrics Educational Foundation sent announcements of its Lectureship program for 1960 to pediatric departments and unaffiliated children's hospitals with a teaching program for residents, inviting requests for Lectureships for the coming year.

The number of *Domestic Lectureships* to meet specific teaching, scientific, and organizational needs and desires has been increased to six, as a result of the experience of the past two years.

The Foundation is happy to announce that Dr. John Lind, Professor of Pediatrics at the University of Stockholm and Chief of Staff of the Karolinska Children's Hospital, will be the *Foreign Lecturer* in 1960. He will spend several weeks in the fall of next year as Lecturer at a number of medical schools.

The Lectureships are available to the pediatric departments of the medical schools in the United States and Canada and to qualified children's hospitals.

BORDEN S. VEEDER *Pediatric Statesman*

Co-editor	*1932-1947*
Editor	*1948-1958*
Editor Emeritus	*1959-*

Founding Member of American Academy of Pediatrics *1932*
President *1942-1943*

Founding Member of American Board of Pediatrics *1933*
President *1934-1941*

President of American Pediatric Society *1935*
President of National Board of Medical Examiners *1946-1950*

Professor of Clinical Pediatrics, Washington University School of Medicine *1917-1951*
Professor Emeritus *1951-*